THE NEUROLOGICAL TRADITION OF THE LONDON HOSPITAL

or

The Importance of Being Thirty*

Sir RUSSELL BRAIN
Bt., D.M. Oxon., D.C.L., LL.D., F.R.C.P.
PHYSICIAN TO THE LONDON HOSPITAL AND THE MAIDA VALE HOSPITAL

Parkinson and "The Shaking Palsy"

THE neurological history of the London Hospital begins in 1776 with the admission of JAMES PARKINSON as a "dressing pupill". This was the James Parkinson (1755–1824) who was to give his name to the syndrome parkinsonism.

His father, John Parkinson, was an apothecary and surgeon living in Shoreditch. It is not known where James was born, but he lived and practised at 1, Hoxton Square, in a house which is now demolished. We owe to Dr. A. D. Morris, till recently medical superintendent at St. Leonard's Hospital, Shoreditch, the discovery that he was a pupil at The London. The minutes of the house committee show that he was admitted on Tuesday, Feb. 25, 1776, for the ensuing six months.

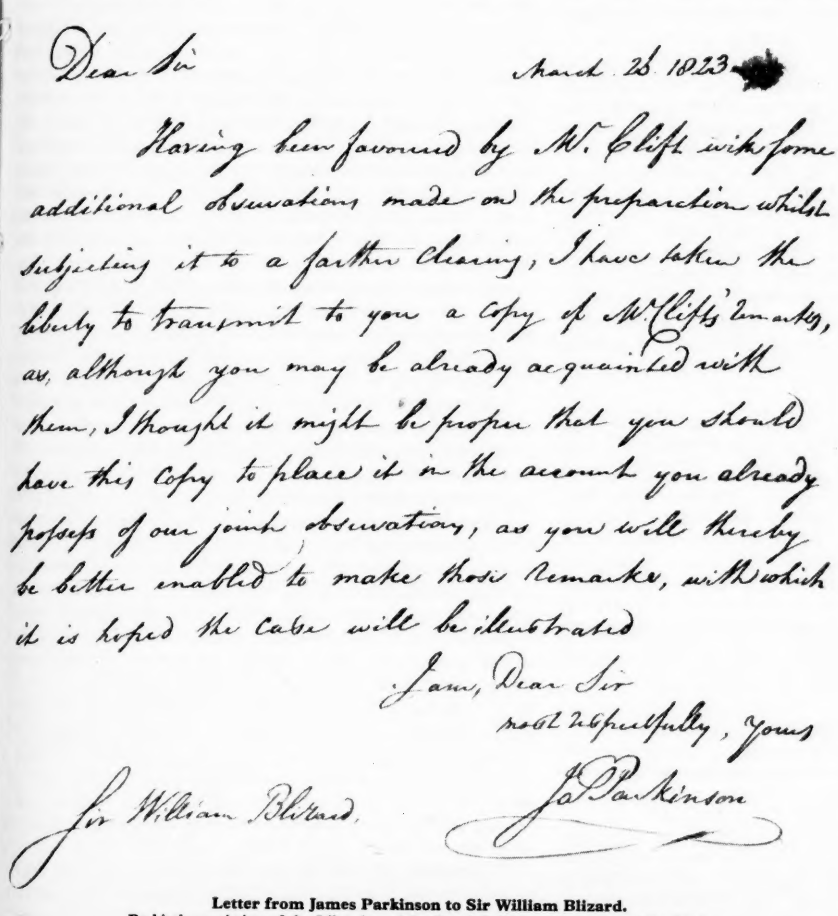
*The Schorstein memorial lecture for 1959, delivered at the London Hospital on Oct. 8.

The evidence that the James Parkinson admitted as a pupil here is the same James Parkinson who subsequently practised in Shoreditch, is, I think, conclusive. One of the five members of the house committee who admitted him was Mr. (later Sir) William Blizard, and Blizard was the surgical consultant to whom James Parkinson turned when he needed expert help. Parkinson (1814) reported a case of hydrophobia. He called in Blizard, who took the patient into The London, where she died in spite of being seen by all the medical and surgical staff. James had a son John whom he sent to The London, and they both figure in the minutes of the London Hospital Medical Club. John Parkinson, Jr, contributed to the report of "a case of recovery after the shaft of a chaise had been forced through the thorax" published by another London Hospital surgeon, William Maiden (1824), and James Parkinson wrote to Sir William Blizard about this patient (see figure).

James Parkinson was a remarkable man, a prolific writer, a scientific controversialist, and a political pamphleteer. He was a member of some of the radical societies which came into existence in this country in sympathy with the French Revolution, and on one occasion gave evidence at a Privy Council inquiry preliminary to the trial of some of his friends for high treason, and there crossed swords with William Pitt. He wrote several popular books on medical topics before the one which ultimately made him famous (McMenemey 1955).

His *Essay on the Shaking Palsy* (1817) is a classic because it is a masterpiece of clinical observation, differentiating in this way what we now call parkinsonism from other disorders associated with tremor. In the absence of any scientific pathology, however, Parkinson's ideas concerning its pathogenesis were necessarily speculative. Having come to the erroneous conclusion that it was due to a disorder of the spinal cord in the cervical region, he was led into some interesting but irrelevant observations on injuries and other disorders of this part of the cord. However, he well recognised his limitations, and at the end of his essay he said:

"Before completing these pages, it may be proper to observe once more, that an important object proposed to be obtained by them is, the leading of the attention of those who humanely em-


Dear Sir

March 25 1823

Having been favoured by Mr. Clift with some additional Observations made on the preparation whilst subjecting it to a farther Clearing, I have taken the liberty to transmit to you a Copy of Mr. Clift's Remarks, as, although you may be already acquainted with them, I thought it might be proper that you should have this Copy to place it in the account you already possess of our joint Observations, as you will thereby be better enabled to make those Remarks, with which it is hoped the Case will be illustrated

I am, Dear Sir
most respectfully, Yours

Jas Parkinson

Sir William Blizard.

Letter from James Parkinson to Sir William Blizard.
By kind permission of the Librarian of the Royal College of Surgeons of England.

ploy anatomical examination in detecting the causes and nature of diseases, particularly to this malady. By their benevolent labours its real nature may be ascertained, and appropriate modes of relief, or even of cure, pointed out."

Here he was obviously anticipating the neuropathologist —and should we not now perhaps add the neurosurgeon?

Parkinson's accuracy of observation and clarity of thought were not limited to medicine. In those days when science was still within the scope of the amateur, he made a name for himself by pursuing geology as a hobby, and he is still commemorated in geological circles by fossils which bear his name.

Parkinsonism returned to The London in a new form when encephalitis lethargica made its appearance just a century after Parkinson published his essay, and ten years later Sir ARTHUR MACNALTY (1927), who had been medical registrar here, published his book, *Epidemic Diseases of the Central Nervous System*, in which his account of encephalitis was based largely on cases seen in Sir Henry Head's wards at The London.

Great Victorians

WILLIAM JOHN LITTLE (1810–94) made such important contributions to orthopædics that Bick (1948) in his *Source Book of Orthopædics* describes him as " the eminent British surgeon ". He was, of course, a physician, and he was born in Aldgate at the house which is now the Old Red Lion and surmounts one of the entrances to Aldgate East station.

He began his medical career as apprentice to an apothecary in East London and a student at the London Hospital. After qualifying he went into general practice. He then spent some time in Germany. Little himself suffered from talipes, said to be due to poliomyelitis, and he persuaded Stromeyer to perform tenotomy of his tendo Achillis. The results were so satisfactory that he stayed at Hanover to learn the technique himself. In 1837 he returned to London, and two years later was elected to the staff of the London Hospital. He was interested in deformities of all kinds, and drew upon a vast experience, including an appointment at the Asylum for Idiots at Reigate. He wrote a monograph on club foot (Little 1839).

His classic description of spastic diplegia, which came to be known as Little's disease, appeared in *The Lancet* in 1843 (Little 1843), among his lectures on deformities —all by the age of 33.

He was as interested in the pathogenesis and prevention of congenital abnormalities as in their treatment, and he emphasised the causal importance of " premature birth, difficult labours, mechanical injuries during parturition to head and neck, where life has been saved following the act of birth " (Little 1862). It was Little the physician who founded the Orthopædic Infirmary which shortly afterwards became the Royal Orthopædic Hospital.

JOHN LANGDON HAYDON LANGDON-DOWN (1828–96), who was my wife's grandfather, came to London from his native Cornwall with the intention of becoming a scientist.

He worked for a time with Faraday, but his health broke down and he spent two years in Devonshire. After his father's death, he decided to take up medicine, and became a student at The London in 1853. After qualifying in 1858, he was appointed medical superintendent of the Earlswood Asylum for Idiots, and in the next year he was elected assistant physician here. Thereafter he combined his work as physician to this hospital with a specialist practice in mental deficiency, and he left Earlswood to found his own private home, Normansfield, in 1868.

His best-known contribution to medicine is his recognition and description of the variety of mental deficiency which he called mongolism in his paper on Ethnic Classification of Idiots, published in the *London Hospital Reports* (Down 1866). His idea was that certain types of mental defective exhibited the physical characteristics of certain races of mankind.

Many years later this hypothetical racial explanation of mongolism was greatly elaborated by FRANCIS GRAHAM CROOKSHANK (1873–1933) in his book *The Mongol in our Midst*. Crookshank, who was not a London Hospital student, but held a post as registrar here for a time, maintained that the mongol type of mental defective never occurred in a race which had no Mongolian strain in it. This is untrue, since it is found in all races of mankind, including the pure Negro stock. It is also of course recognised in the Mongolian races, and is now known in the Soviet Union as Langdon-Down's disease. Its cause remained mysterious until this year, when three groups of workers, Lejeune et al. (1959), Ford et al. (1959), and Jacobs et al. (1959) showed that it is associated with the presence of an extra somatic chromosome. Jacobs et al. suggest that this observation, considered in relation with the well-known fact that the risk of giving birth to a mongol is closely related to increasing maternal age, and that the mongol child resembles its mother antigenically more closely than its father, indicates that the primary disorder may lie in oogenesis.

Langdon-Down's book *Mental Affections of Childhood and Youth* is still well worth reading for its wealth of clinical observations. In it he gives a very detailed clinical account of adiposogenital dystrophy forty years before Fröhlich, though Langdon-Down said nothing about its pathogenesis. He was a liberal-minded man who in more than one respect was in advance of his time. He vigorously defended the higher education of women, and denied that it made them more liable to produce feebleminded offspring. He drew a rather surprising conclusion from his ethnic classification of idiots, maintaining that if a mentally defective member of a white race could show the racial features of a non-white race, it proved that racial differences were not specific; and he used this argument obliquely to refute the apologists for Negro slavery in the Southern States at the time of the American Civil War.

Sir JONATHAN HUTCHINSON (1828–1913) was a remarkable figure, even in that remarkable age. A Yorkshireman of Quaker stock, he studied first in the York School of Medicine, and then at St. Bartholomew's Hospital. He was elected assistant surgeon to The London at the age of 31. In addition, he was surgeon to the City Hospital for Chest Diseases and the Metropolitan Free Hospital, to the Blackfriars Hospital for Skin Diseases, and to Moorfields Hospital—general surgeon, dermatologist, syphilologist, ophthalmologist, and neurologist. His first paper was published in 1852, when he was about 24, his last in 1911, nearly sixty years later. During that time he must have published at least fifteen hundred communications, and for eleven years he was himself alone responsible for the annual appearance of the *Archives of Surgery*. His classical contributions to our knowledge of congenital syphilis were contained in a paper on the teeth, published in 1858, when he was 30 (Hutchinson 1858a), and a series of papers on the eye, published during the next two years (Hutchinson 1858b, 1859, 1860).

He attained general recognition as a neurologist, and became president of the Neurological Society. His papers on head injury are classics of clinical observation (Hutchin-

son 1867). The first volume of *Brain* contains a long contribution from his pen on the pupils, in which as both a neurologist and an ophthalmologist he was particularly interested (Hutchinson 1878), as he was also in optic neuritis, on which he wrote many papers. As neurologist and syphilologist he wrote a good deal on neurosyphilis, but before the discovery of the treponema and the Wassermann reaction this was necessarily somewhat speculative. For example, he includes among the possible causes of tabes standing with one's back to the fire—perhaps a warning, or possibly an alibi, for the Victorian paterfamilias (Hutchinson 1880). His interest in diseases of the blood-vessels extended to occlusion of the internal carotid artery, intracranial aneurysm, and temporal arteritis, which he seems to have been the first person to describe. Hutchinson's lifelong friendship with Hughlings Jackson, who before his marriage shared his home, had a profound influence on both men.

As a pleasant footnote to Jonathan Hutchinson it is worth recording that his son JONATHAN HUTCHINSON, Jr., also surgeon to the London Hospital, described congenital fusion of the cervical vertebræ in 1894, eighteen years before Klippel and Feil, with whose names it is now associated (Hutchinson 1894).

There are some discoveries which so reflect the character of those who make them that we come to feel that they could hardly be made by anyone else. There are others which seem so accidental that almost anyone, we think, given the same opportunities, might have made them; but then other people did not. This deceptive ease characterises the discoveries of WAREN TAY (1844–1927). He was a Yorkshireman who became the devoted disciple of Jonathan Hutchinson, whose house for a time he shared. He joined the staff of The London in 1869 at the age of 25. Those were the days when what we now call general medicine or general surgery would have seemed a narrow specialty. Tay was both general surgeon and ophthalmic surgeon at The London. He also became assistant surgeon to the Hospital for Diseases of the Skin at Blackfriars, and in those days there was no very clear distinction between physician and surgeon in dermatology. As a dermatologist he translated Hebra's book on diseases of the skin. He was also a surgeon at Moorfields, and at what is now the Queen Elizabeth Hospital for Children. He was one of the founders of the Ophthalmological Society, and it was in the first volume of its *Transactions* that he described "symmetrical changes in the region of the yellow spot in each eye of an infant", which was the first account of the retinal appearances in amaurotic family idiocy (Tay 1881). Later he reported another case from the same family, thus establishing its familial incidence (Tay 1884). The pathology of the disorder was later described by Bernard Sachs (Sachs 1887). Hence the name Tay-Sachs disease.

Tay was a kindly, shy, retiring bachelor whose hobby was tricycling. He did a great deal of work for and in collaboration with Jonathan Hutchinson. There is an illuminating story concerning the other retinal abnormality which is associated with Tay's name. He said one day: "Why do they call it Tay's choroiditis?" Someone said: "But didn't you discover it?" "Oh yes," he said, "I did see it first, but Mr. Hutchinson gave it a name." It is worth recalling that Tay's observations were made with an ophthalmoscope which depended upon reflecting into the eye by means of a mirror light from an oil lamp.

JOHN HUGHLINGS JACKSON (1835–1911) was a Yorkshireman who began to learn medicine as apprentice to a doctor in York and a pupil at the York Medical and Surgical School. He qualified at St. Bartholomew's, and returned to York as house-surgeon to the Dispensary. He then nearly gave up medicine to devote his life to writing, and particularly to philosophy, but he came to London with an introduction to Jonathan Hutchinson, a fellow Yorkshireman, who dissuaded him from this course. No doubt it was through Hutchinson's influence that Jackson, exactly a hundred years ago, came to The London as lecturer in pathology, and in 1863 he was appointed assistant physician here, and lecturer on physiology at the medical college. It was Brown-Séquard, however, who attracted him to neurology, and Jackson joined the staff of the National Hospital, Queen Square, in 1862, two years after its foundation.

His greatness springs from the happy combination of two mental qualities. He was first a great clinical observer. He listened to what the patient said in describing his symptoms, and he looked with an eye for the minutest detail at his physical signs. Because of this attentiveness, he observed many things which had previously escaped notice. Jackson worked at Moorfields and was one of the first physicians to use the ophthalmoscope and to draw attention to the diagnostic importance of optic neuritis, as papillœdema was then called; and he insisted on the importance of examining the optic fundi "in all cases of severe cerebral disease" because optic neuritis might be present without the patients' having noticed any impairment of vision.

But observation by itself, though it might have led Jackson to describe some new syndromes, would never have made him the great man he was. Having observed he reflected. He had the mind of a philosopher, and Jonathan Hutchinson (1925) once wondered whether he had been right to persuade Jackson to stick to medicine, or whether the world at large might not have been better off if he had been left to devote his mind to philosophy.

It is not easy to summarise Hughlings Jackson's contributions to neurology. His name is particularly associated with that type of focal epilepsy now known as jacksonian—though, as Jackson himself recognised, it had been first described by Bravais in 1824. His views on epilepsy can be briefly summarised in his own words: "A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles" (Jackson 1931). All recent research on epilepsy has lent support to this view.

Even as lately as forty years ago, there was little beyond clinical observation to differentiate the varieties of epilepsy; and in many cases, the cause being unknown, the patient was regarded as suffering from idiopathic or cryptogenic epilepsy. Since then clinical observation has been reinforced by air encephalography and ventriculography, angiography, and above all electroencephalography and electrocorticography, which have enabled us to localise the lesions responsible for what in the past was described as just epilepsy, or idiopathic epilepsy; this in turn has stimulated the study of such lesions by the pathologists. The recognition that epilepsy, much more often than used to be thought, is the symptom of a focal cerebral lesion has left us with a more clearly demarcated group of patients suffering from "central epilepsy" comprising chiefly "idiopathic" grand mal and petit mal, the nature of which is still not fully understood, but which probably has a different pathogenesis from the epilepsy resulting from acquired focal lesions.

The study of epilepsy raised in Jackson's mind many questions regarding the origin and spread of the epileptic discharge and the mode of representation of the parts of the body in the nervous system. It is worth recalling that all his observations on focal convulsions were made, and the conclusions drawn from them, before they were con-

firmed, as far as they could be by animal experiment, by the researches of Fritsch, Hitzig, and Ferrier.

Jackson was a pioneer also in the study of speech disturbances, and pointed out that it was inaccurate to say that a patient who could not speak because he was aphasic had lost the use of words. Though words were not available to him when he wanted to express his meaning, he might still be able to swear. Jackson's views on speech were not generally accepted, because they conflicted with the simple but crude notions of speech psychology and physiology which were popular with those workers whom Head was later to call " the diagram-makers "; but they are beginning to come into their own today. It was Jackson who first recognised agnosia, which he called imperception, and apraxia.

His most philosophical contribution to neurology was his conception of the evolution and dissolution of the nervous system. It followed from his idea of the organisation of the nervous system that the symptoms observed after a lesion could not be produced by the part which has been destroyed but must be the result of activity of surviving parts of the brain, which in many cases are to be regarded as having been released from some kind of higher control. This idea has had a very wide application in the interpretation of the symptomatology of nervous disease, and Jackson's views greatly influenced the subsequent researches of Sherrington.

With Hughlings Jackson's reflectiveness went a certain absent-mindedness which the public is apt to associate with those who are much absorbed by their own thoughts, and it is recorded of him that he could never find his way to his own wards in hospital without a guide. He exhibited many of the amiable eccentricities of genius.

James Taylor (1925) tells how " on one occasion he bought at a railway bookstall, when he was about to start on a journey, a novel in the days of the old ' yellow backs '. His first action was to tear off one of the boards and then the other and throw them away. He next proceeded to tear the book in two, putting one half in one pocket and the other in the other. The bookstall boy stood staring at him open-mouthed, and Jackson, seeing this, said to the boy in his usual quiet way: ' You think I am mad, my boy, but it is the people who don't do this who are really mad.' "

Jonathan Hutchinson (1925) relates that when Jackson was to be elected assistant physician here he forgot to attend the meeting and Hutchinson had to persuade an obliging secretary to keep the quorum whilst he took a hansom cab and hunted him up.

There are many examples of his sense of humour.

In one of his papers he illustrated a condition of impaired consciousness by the story of a man who went to sleep during the sermon in church, and being partially awakened by the arrival of the collection murmured " Season ".

When the first operation for a brain tumour was performed by Rickman Godlee at the Maida Vale Hospital, Jackson was present. The patient was a Scotsman, and at the end Jackson said to Godlee: " You've missed a great opportunity. You have opened a Scotsman's head and neglected to put a joke in."

Jackson married his cousin, and they had no children. She died at the age of 39 of a cerebral illness which, by a strange irony, caused convulsions of the type associated with her husband's name. His brother went to New Zealand, where his great-nephew is now a doctor.

Henry Head and his Collaborators

Sir HENRY HEAD (1861–1940) came of Quaker stock. His maternal grandfather, Richard Beck, was a partner in the wine business of his uncle J. J. Lister, who was Lord Lister's father. The Heads and the Listers were therefore cousins.

Henry Head was at Trinity College, Cambridge, where the philosopher Whitehead (1948) recalls him as one of his outstanding contemporaries. After taking a first class in the second part of the natural sciences tripos, with physiology and comparative anatomy as his subjects, Head decided to work abroad, and spent some time with Hering at Prague on the physiology of respiration. He then went to University College Hospital where he qualified. It may have been his interest in respiration which led him to obtain a post at the City of London Hospital for Diseases of the Chest.

His first major contribution to neurology arose out of his experience of general medicine, for between 1893 and 1896, when he was between 32 and 35, he published in *Brain* a series of articles amounting to 400 pages beginning with his Cambridge thesis on Disturbances of Sensation with especial reference to the pain of visceral disease (Head 1893, 1894, 1896). I have reprints of these papers bound together as one volume which Head gave to Schorstein. They are still worth reading, especially by the general physician. Head was appointed medical registrar at the London Hospital in 1896 and within four months elected assistant physician.

No doubt Head's early work on pain directed his interest into the field of sensation in general, and in the early years of this century he was investigating peripheral-nerve injuries in collaboration with JAMES SHERREN, who was on the surgical staff here. Sherren (1872–1945), who had been at sea and taken his master mariner's certificate before beginning medicine, was later to become well known as an abdominal surgeon. Head and Sherren's work on peripheral-nerve injuries was published in *Brain* (1905) and formed the basis of a book on *Injuries of Nerves and their Treatment*, by Sherren (1908). Head and Sherren found, however, that their study of peripheral-nerve injuries had raised questions which could not be answered by observations made on patients, since they required more time and introspection than could be expected of the average hospital patient. They therefore decided to make the famous " human experiment in nerve division ", and the radial and external cutaneous nerves in Head's left forearm were divided and re-sutured.

W. H. R. Rivers, who was not only medically qualified but also a psychologist and anthropologist, carried out the subsequent sensory testing. The outcome of this experiment was the famous division of peripheral sensory fibres into the " protopathic " and the " epicritic ", which Head and Rivers believed owed their separate origin to the evolutionary development of the nervous system.

I have a pleasant memento of this " human experiment in nerve division " in two volumes of Thomas Watson's *Lectures in the Principles and Practice of Physic*, on the flyleaf of which Head has written: " These volumes were given me by my friend W. H. R. Rivers in memory of our ' Human Experiment in Nerve Division'. For, during these observations, they used to lie beside me in his rooms to refresh me in the intervals of rest."

From the peripheral nerves Head moved to the spinal cord to try to discover how the various forms of sensation mediated by the peripheral nerves were organised when they reached the cord. This work was carried out in collaboration with THEODORE THOMPSON (1878–1935).

Thompson, like Head a Cambridge graduate, was a man of outstanding intellectual ability, who took in his stride the London B.SC. and the F.R.C.S. before becoming assistant physician here in 1907. He was known as " the Turtle " on account of his rotund build and somewhat rolling gait, and this appearance was accentuated by the fact that he frequently wore a tail-coat. Thompson was an outstandingly good diagnos-

tician, but his interests were clinical in a wide field which included pædiatrics, and he made no further important contribution to neurology.

Continuing his studies of sensation, now in collaboration with Sir Gordon Holmes, Head made his classical contributions on the sensory functions of the optic thalamus and the cerebral cortex, which he sought to associate again with protopathic and epicritic sensibility respectively (Head and Holmes 1911–12).

Meanwhile, the first world war had produced large numbers of patients suffering from injuries of the nervous system at all levels. In his researches into these Head was joined by a young Aberdonian, GEORGE RIDDOCH (1888–1947).

Riddoch, having qualified at Aberdeen in 1913, came to London as a resident at the West End Hospital for Nervous Diseases, where he worked with Purves-Stewart. When the war broke out he became officer in charge of the Empire Hospital for Injuries of the Nervous System, Vincent Square, and there he met Henry Head.

They collaborated in the investigation of patients with severe injuries of the spinal cord, studying particularly the automatic bladder, excessive sweating, and the generalised reflex response to stimulation which they termed the "mass reflex" (Head and Riddoch 1917).

Head's other major interest was aphasia.

In this field he adopted a dynamic and psychophysiological approach derived from Hughlings Jackson. His two volumes on aphasia were not published until 1926 (Head 1926), when he had already been suffering from parkinsonism for some years. They are a major contribution to the subject, illuminated by flashes of insight, but lacking in some respects the constructive vigour of his earlier work.

This is not the occasion on which to attempt a critique of Head's contribution to neurology. It is easy to find details to criticise. He was an imaginative man, and sometimes his imaginative hypotheses ran away with him. But ideas are not so plentiful that we ought to complain if a man who has some good ones has some bad ones too. Head's contribution to neurology is safe, both for what he did himself and for his stimulating effect upon others. Turnbull (Hunter 1955) has left a vivid account of him as a teacher.

"In his rounds of the wards his clerks read the histories and examinations they had written, and he criticized even the English. He did not confine himself to nervous diseases, but took more pains than any other physician for whom I clerked to teach us physical signs and how to examine patients of all kinds. He was a great man."

The fourth volume of *Munk's Roll* of the fellows of the Royal College of Physicians describes him as "a teacher of infectious enthusiasm and vitality, who combined a scientific outlook with a vivid imagination; a large, rotund figure with beard and moustache and a voice that became falsetto in moments of excitement".

I have spoken of his parkinsonism, which his friends first noticed twenty years before his death. Grantly Dick-Read told me that shortly after the first world war Head invited him to a meal. Dick-Read preceded Head into the dining-room, and, hearing his shuffling footsteps behind, looked round. Head said, "Ah, I see that I have taught you too well!" The last time I saw Head was when I spent a day with him less than a year before he died. He was then completely immobile, and had great difficulty in talking, but he was intensely interested in his symptoms, and his mind was as wide-ranging as ever.

We talked among other things about the body image and projection. He quoted Lotze as saying that "a woman can project to the end of the feather in her hat", and added: "a well-made dental plate is part of one's body, but if you get a pip under it, it becomes a foreign body".

Head was a man of imagination and sensibility, a friend of poets, and himself a poet. When he retired from practice he went to live in Dorset as Thomas Hardy's neighbour. His book of poems, *Destroyers*, stands on my shelf beside Sherrington's verses, *The Assaying of Brabantius*. I enjoy them both, but I think that Head was the better poet. I cannot sum him up better than in the words of the late Robert Nichols (1940), himself a poet, and a friend of Head's and of mine, who wrote of him:

"Sir Henry possessed the fullest as well as the wisest mind I have ever known. It was no unusual thing to hear him in the course of one evening discourse on topics so various as: the influence of reasoning upon Goethe and Mozart, types of apprehension in listeners to symphonic music, sensations while looping the loop (he was over sixty when he did so), the painting of Guardi, 'coordination' in a star golfer, Ninon de Lenclos, Conrad as narrator (Sir Henry was far the ablest literary critic I have ever known), religious ecstasy, the relation of art and science, the social customs of Melanesia . . . truly a noble spirit, just as wise and calm as kind; a kind of Quaker Prospero."

EDWIN GREAVES FEARNSIDES (1883–1919) was a Yorkshireman who qualified at the London Hospital and became one of Head's pupils. He published a paper with Head on clinical aspects of neurosyphilis (Head and Fearnsides 1914–15) and one on intracranial aneurysms (Fearnsides 1916), which was primarily a pathological study, based on material collected over a number of years in the pathological institute. Fearnsides was appointed to the staff of Maida Vale Hospital in 1913. He was a man of great promise whose life was tragically cut short by a boating accident when he was only 36.

GEORGE RIDDOCH made an independent study of the reflex functions after spinal-cord injury (Riddoch 1917a) and also of disturbances of vision after injuries involving the occipital lobe (Riddoch 1917b). The end of the war found him still under 30, and with an established reputation as a neurologist. Within a year he had been elected to the staff of the Maida Vale Hospital, and a year later he joined the newly formed medical unit at the London Hospital as first assistant. At that time there was a dearth of young neurologists. Riddoch was offered an appointment on the staff of another teaching hospital, and, rather than let him go, The London created a vacancy for him and he was elected assistant physician in 1924. He was such a good doctor that he was rapidly overwhelmed with practice, and apart from one or two papers, notably a contribution to a book on the hypothalamus (Riddoch 1938a), his Lumleian lectures on pain of central origin (Riddoch 1938b), and his presidential address to the Neurological Section of the Royal Society of Medicine on phantom limbs (Riddoch 1941), his original contributions to neurology came to an end when he was 35. But the unrivalled experience of the care of paraplegics which he gained during the first world war proved of great value in the second, when as consultant neurologist to the Army he was responsible for organising units for the treatment of paraplegia.

In trying to assess George Riddoch as a man and a doctor I do not think I can do better than repeat some words which I used at the time of his death.

"He was not much interested in abstract philosophy, but he was a practical exponent of the philosophy of organism, the

physiological philosophy which he inherited from Hughlings Jackson and Henry Head. He applied it to the simplest neurological phenomena. However disease may dissect the nervous system, the living organism works as a whole; and he would point out that even in the spinal animal a reflex response is not stereotyped, but is influenced by the pre-existing posture of the limb, so that what is left of the nervous system still acts as a whole; and from the spinal cord to the cerebral cortex the same principle operates. This sense of the wholeness of man meant taking into account the mind as well as the body, and it was part of his excellence as a doctor that he was always in the broad sense a psychiatrist, a healer of minds . . . Riddoch's place in neurology is secure, even though the very plenitude of his gifts came to favour the doctor at the expense of the investigator. . . . His friends will recall his gaiety and humour, his stories, many of them Aberdonian, which set the table in a roar, and at which he laughed himself till he had to wipe his eyes, and in quieter moments his love of fishing and the Rothiemay countryside, birds, books, and above all music."

Neurology from Many Sources

A number of London Hospital men who were not themselves neurologists nevertheless contributed something of importance to neurology. Sir ROBERT HUTCHISON, for example (1907–08), described cases of neuroblastoma of the suprarenal occurring in childhood and producing metastases in the orbits (leading to exophthalmos), and in the long bones—a syndrome now associated with his name.

MARTIN FLACK (1882–1931) was the son of the butcher in the village of Borden in Kent. Sir Arthur Keith (1866–1955), then professor of anatomy at the London Hospital, took a house in the neighbourhood in 1903 just when Flack, having come down from Oxford, was looking for a medical school in London. Keith, hearing this, captured him for The London, and Flack, as an undergraduate demonstrator in physiology, started with Keith to review the recently described auriculoventricular bundle by making a microscopical examination of the heart. One evening Keith came back from a bicycle-ride to find that Flack had discovered in the heart of a mole the structure which came to be known as the sino-auricular node. Their discovery was reported in the *Journal of Anatomy* (Keith and Flack 1907). Flack was 24 at the time.

Sir WILLIAM LISTER (1868–1944), nephew of Lord Lister and cousin of Sir Henry Head, ophthalmic surgeon to the London and Moorfields Hospitals, did pioneer work with Sir Gordon Holmes during the first world war in deducing from the effects of gunshot wounds of the occipital lobes the representation of the visual fields in the cerebral cortex (Holmes and Lister 1916).

HUBERT MAITLAND TURNBULL (1875–1955) was so good a pathologist that it may be said of him that he touched nothing which he did not adorn, and there were few aspects of pathology which he did not touch.

Coming to the London Hospital from Oxford in 1900, he has related how he had the good fortune to meet Henry Head daily in the mornings on the Underground; and to meet Head was to catch something of his contagious enthusiasm. Turnbull's interest in neurology had already been aroused by his studies of anatomy and physiology, and he was further stimulated by the three months he spent as Head's clinical clerk. His D.M. thesis was on a neurological subject, and was published in *Brain* (Turnbull 1904).

His two main contributions to neuropathology were his paper on intracranial aneurysms (Turnbull 1918) which continued the work begun in an earlier paper on Alterations in Arterial Structure, and their relation to syphilis (Turnbull 1915), and his original description of Encephalomyelitis following Vaccination, which he wrote in collaboration with JAMES MCINTOSH (1882–1948) (Turnbull and McIntosh 1926). Turnbull had seen his first case of postvaccinal encephalomyelitis in 1912. His attention was directed to the subject again by the outbreak in 1922 and 1923. The publication of his paper was, through no fault of his own, delayed until 1926, as the result of which he was anticipated by Bastiaanse, who reported a series of Dutch cases in 1925. Nevertheless, postvaccinal encephalomyelitis is known in Germany as *Die Turnbullsche Krankheit*. Turnbull's pathological study of an acute demyelinating disease of the nervous system was the main stimulus which led to the large and growing volume of pathological and experimental work on this subject which is still being done all over the world.

I have already mentioned the difficulty of diagnosing neurosyphilis before the discovery of the Wassermann reaction. The discovery of the spirochæte raised problems of pathology and nosology which were discussed by McIntosh in collaboration with Sir Paul Fildes (McIntosh and Fildes 1914a). They were the first British workers to confirm Noguchi's observation of spirochætes in the brain in dementia paralytica (McIntosh and Fildes 1914b), and with Head and Fearnsides discussed the nature of " parasyphilis " (McIntosh, Fildes, Head, and Fearnsides 1914). Thus this group of workers made a considerable contribution to the clinical, pathological, and serological analysis of neurosyphilis in the comparatively early days of the Wassermann reaction.

Sir HUGH CAIRNS (1896–1952) was not the first of Harvey Cushing's British pupils, but the year he spent with Cushing had a catalytic effect upon British neurosurgery. Cairns, whose only published papers were on congenital cystic kidneys and tumours of the testicle, was elected to the surgical staff of The London at the age of 29, and sent to work with Cushing for a year, to learn neurosurgery. When he came back, the Medical Research Council published his report on his visit, and the contrast between Cushing's results and those obtained by the methods currently in vogue in this country proved startling. With characteristic drive and organising ability Cairns built up the neurosurgical department here, and was soon attracting pupils from many parts of the world.

Hugh Cairns, an Australian Rhodes scholar and Oxford rowing blue, was an active rather than a contemplative man, and he will chiefly be remembered for his part in raising the standard of neurosurgery in this country, with its worldwide effect through his pupils. His widely ranging mind saw that a specialty is not a circumscribed area of knowledge, but a dynamic field of interrelationships with other branches of medicine; and this is exemplified by the research which he and his colleagues at Oxford carried out into the application of antibiotics to the treatment of meningitis, particularly tuberculous meningitis, shortly after the last war.

Age, Research, and Freedom

A tradition may consist merely of the conglomerated facts of the past, or show a continuity of thought and attitude. Though many of the past contributions of Londoners to neurology have had no relation to one another, I think it is possible to distinguish three threads of continuity in the London Hospital tradition. From Jackson, through Head to his collaborators, there is the approach to neurology in terms of physiology combined with the recognition that only the study of disease in man can illuminate human physiology. Closely linked with this is the dynamic and holistic attitude, also springing from Jackson, which is not content to explain the

behaviour of the whole in terms of the parts but claims that even the most fragmentary reactions are influenced by the totality. The third continuing tradition has been the close link between neurology and general medicine.

Our survey has shown the progressive narrowing of specialisation in the last hundred years from the catholicity of a Jonathan Hutchinson, who made no clear distinctions between surgery, medicine, and half a dozen specialties, as we should now call them, to a Riddoch or a Cairns practising in virtually a single subject.

But from Jackson onwards neurologists to The London have remained in some measure general physicians, and the link between neurology and pathology has also been close. Here, I think, by staying in the same place we find ourselves today in advance of the times.

As medical knowledge expands we learn not merely more facts but more relations between facts, and discover that every specialist needs to know more about work in an increasing number of other fields. This looks frightening at the moment because we have been brought up on old-fashioned lines, and have not yet developed the techniques for synthesising, teaching, and learning the new ideas we shall need. Whether we like it or not, this will involve a revolution in medical education. It will also mean that though we shall still need specialties and special hospitals they will be specialties with a closer relation to the rest of medicine than anything we have known since Jonathan Hutchinson's day.

By the accident of time we tend to regard our distinguished predecessors as having always been old men, for it is as old men that their successors recall and portray them. But you cannot have failed to notice the ages at which those we have been recalling today began to make their contributions to knowledge and indeed made some of their most original and important ones, nor the ages at which they achieved consultant status with sole responsibility for their patients. To make this quite clear I have tabulated both (tables I and II).

Making all allowances for the fact that the young consultant has to learn more today than he did thirty years ago, and for other changed social and economic factors, I want in conclusion to ask some questions.

What is the significance of the fact that all these men whose contributions to neurology we acknowledge today were starting to do research before they were 30 and did some of their most original work between the ages of 30 and 35? Is it true in general that a man's most creative period is between the ages of 25 and 35? Whether it is true in general, or only of exceptional men, what opportunities does our present system give for such work at these ages? And if the opportunity is missed, is a man likely to start at 35 to do the work he could have done at 25 or 30? And if even thirty years ago men were held fit for consultant responsibilities at 29 or 30 why are they not so regarded now? Is such fitness to be measured only by clinical experience, slowly accumulating through the routine work of assisting consultants for years? And if only a generation ago it was possible for a hospital to create a post for a good man and invite him to take it, or to pick a Hugh Cairns solely on his personality, put him on the staff first and then make a neurosurgeon of him in a year, are we better off today for having had that freedom taken away from us?

Finally, can the creative spirit, which bloweth where it listeth, be made to conform to the terms and conditions of the Health Service and the regulations governing advisory appointments committees? And, if not, which is the more important?

TABLE I—AGE AT PUBLICATION

Author	Subject	Age	Year
Little	Monograph on club-foot	29	1839
	Description of spastic diplegia	33	1843
Langdon-Down	Description of mongolism	38	1866
Hutchinson	The teeth in congenital syphilis	30	1858
	The eye in congenital syphilis	30–32	1858–60
Tay	Amaurotic family idiocy	37	1881
Jackson	Jacksonian epilepsy	28–35	1863–70
Head	Pain of visceral disease	32–35	1893–96
Flack	Sinoauricular node	24	1907
Riddoch	War injuries of nervous system	28	1917

TABLE II—HOSPITAL APPOINTMENTS

Name	Consultant appointment	Age	Year
Little	London Hospital	29	1839
Langdon-Down	" "	31	1859
Hutchinson	" "	31	1859
Tay	" "	25	1869
Jackson	" "	28	1863
Head	" "	35	1896
Thompson	" "	28	1907
Fearnsides	Maida Vale	30	1913
Riddoch	" "	30	1919
	London Hospital	35	1924
Cairns	" "	29	1926

Average age = 30.

REFERENCES

Bick, E. M. (1948) Source Book of Orthopædics. Baltimore.
Crookshank, F. G. (1921) The Mongol in our Midst. London.
Down, J. L. (1866) *Clin. Lect. Rep. med. surg. Staff London Hosp.* **3**, 259.
— (1887) On Some of the Mental Affections of Childhood and Youth. London.
Fearnsides, E. G. (1916) *Brain*, **39**, 224.
Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. (1959) *Lancet*, i, 709.
Head, H. (1893) *Brain*, **16**, 1.
— (1894) *ibid.* **17**, 339.
— (1896) *ibid.* **19**, 153.
— (1926) Aphasia and Kindred Disorders of Speech. Cambridge.
— Fearnsides, E. G. (1914–15) *Brain*, **37**, 1.
— Holmes, G. (1911–12) *ibid.* **34**, 102.
— Riddoch, G. (1917) *ibid.* **40**, 188.
— Rivers, W. H. R. (1908) *ibid.* **31**, 323.
— Sherren, J. (1905) *ibid.* **28**, 116.
— Thompson, T. (1906) *ibid.* **29**, 537.
Holmes, G., Lister, W. T. (1916) *ibid.* **39**, 34.
Hunter, D. (1955) *Lond. Hosp. Gaz.* **58** (suppl. to December issue).
Hutchinson, J. (1858a) *Trans. Path. Soc. Lond.* **9**, 449.
— (1858b) *Roy. Lond. Ophth. Hosp. Rep.* **1**, 191, 226.
— (1859) *ibid.* **2**, 54.
— (1860) *ibid.* **3**, 258.
— (1867) *Clin. Lect. Rep. med. surg. Staff Lond. Hosp.* **4**, 10.
— (1878) *Brain*, **1**, 1, 13, 155, 454.
— (1880) *Med. Times Gaz.* **1**, 23.
— (1925) *in* Neurological Fragments, by J. Hughlings Jackson. London.
Hutchinson, J., Jr. (1894) *Brit. med. J.* i, 634.
Hutchison, R. (1907–08) *Quart. J. Med.* **1**, 33.
Jackson, J. H. (1931) Selected Writings, 1.
Jacobs, P., Baikie, A. G., Brown, W. M. C., Strong, J. A. (1959) *Lancet*, i, 710.
Keith, A., Flack, M. (1907) *J. Anat.* **41**, 172.
Lejeune, J., Gauthier, M., Turpin, R. (1959) *C.R. Acad. Sci., Paris*, **248**, 602.
Little, W. J. (1839) Treatise on the Nature of Clubfoot and Analogous Distortions. London.
— (1843) *Lancet*, i, 350.
— (1862) *Trans. obstet. Soc., Lond.* **3**, 293.
Maiden, W. (1824) An Account of a Case of Recovery after the Shaft of a Chaise had been Forced through the Thorax. London.
McIntosh, J., Fildes, P. (1914a) *Brain*, **40**, 141.
— — (1914b) *ibid.* **37**, 401.
— — Head, H., Fearnsides, E. G. (1914) *ibid.* **36**, 1.
McMenemey, W. (1955) *in* James Parkinson (edited by Macdonald Critchley). London.
MacNalty, A. S. (1927) Epidemic Diseases of the Central Nervous System. London.
Nichols, R. (1940) *Times*, Oct. 10.
Parkinson, J. (1814) *London med. surg. pharm. Reposit.* **1**, 289.
— (1817) An Essay on the Shaking Palsy. London.
Riddoch, G. (1917a) *Brain*, **40**, 16.
— (1917b) *ibid.* 264.
— (1938a) The hypothalamus (by le Gros Clark, Beattie, Riddoch, and Dott).
— (1938b) *Lancet*, i, 1093, 1150, 1205.
— (1941) *Brain*, **64**, 197.
Sachs, B. (1887) *J. nerv. ment. Dis.* **14**, 541.
Sherren, J. (1908) Injuries of Nerves and their Treatment. London.
Tay, W. (1881) *Trans. ophth. Soc.* **1**, 55.
— (1884) *ibid.* **4**, 158.
Taylor, J. (1925) *in* Neurological Fragments, by J. Hughlings Jackson. London.
Turnbull, H. M. (1904) *Brain*, **27**, 209.
— (1915) *Quart. J. Med.* **8**, 201.
— (1918) *Brain*, **41**, 50.
— McIntosh, J. (1926) *Brit. J. exp. Path.* **7**, 181.
Whitehead, A. N. (1948) Essays in Science and Philosophy. London.

TOLBUTAMIDE CONTROL OF DIABETES MELLITUS

SELECTION OF PATIENTS AND PERSISTENCE OF RESPONSE

G. F. JOPLIN
M.B. N.Z., M.R.C.P.
MEDICAL TUTOR

RUSSELL FRASER
M.D. N.Z., F.R.C.P.
PROFESSOR OF CLINICAL ENDOCRINOLOGY

J. VALLANCE-OWEN *
M.A., M.D. Cantab., M.R.C.P.
LATE MEDICAL TUTOR

POSTGRADUATE MEDICAL SCHOOL OF LONDON, W.12

WHILE tolbutamide is now firmly established as a useful drug for the treatment of some mild diabetics, it remains difficult to select patients who will respond to it. Tolbutamide is generally agreed not to control diabetics who are liable to ketosis, and it is, therefore, rarely satisfactory for patients who are thin or under 40 at the onset of their illness. Another large group can be controlled by diet alone. It is for some of the intermediate group, who are neither liable to ketosis nor controllable by diet alone, that tolbutamide may be useful; but no reliable criteria have yet been established for their selection.

In this paper we shall describe an outpatient trial procedure for selecting diabetics suitable for tolbutamide control, as well as our studies of the persistence of their response.

Material and Method

Clinical Material

The first 58 available and suitable mild diabetics in this department were tried—i.e., those without known ketosis, free of chronic infection, needing less than 40 units of insulin and capable of careful tests. Any necessary weight reduction had first been achieved or had proved hopeless. We had previously tested another 7 mild cases which had shown ketosis and had confirmed the unresponsiveness of this group (American Diabetes Association 1957).

Method

The initial trial was designed to be as short and as simple as is compatible with validity. As patients taking tablets and testing their urine thrice daily pay stricter attention to diet, periods on placebo tablets had to be incorporated to avoid ascribing incorrectly any of this improvement to tolbutamide.

Patients previously on insulin recorded Acetest and Clinitest tests on urine passed before breakfast, lunch, and supper. Insulin was not discontinued until the home testing and recording agreed with the duplicate specimens tested by the clinic, and the optimal control on insulin and diet was obtained. Then forty-eight hours' withdrawal of insulin before a clinic visit identified most of the potentially ketotic cases: these were at once returned to insulin. If diabetic symptoms had appeared, tolbutamide was begun at once and the patient was reviewed in a few days.

All the others, including those not yet on insulin, were started on placebo tablets. If the placebo phase confirmed the absence of ketosis and the need for better control, the patients were then passed through at least four alternating fortnightly periods of placebo and tolbutamide tablets. The tolbutamide was given at the standard dosage of 0·5 g. four times daily. During each fortnightly period the efficacy of treatment was assessed from the mean result of the second week's twenty-one home urine tests and a fasting blood-sugar at the end of the period. Observations continued until at least two periods of each type had been satisfactorily observed.

The blood-sugars were estimated first by Harding's modification of the Schaffer-Hartman method (King and Wootton 1956), and later by the method of Huggett and Nixon (1957). Throughout the two years of this outpatient study, three duplicate specimens in each batch were estimated "blind" in the routine biochemical laboratory. From 100 pairs of duplicates by the first and 44 pairs by the second method we have estimated the standard error of single estimations to be 2·02% and 1·85% respectively.

From their response to treatment in each of the four fortnightly periods, patients could be classified into four groups:

1. *Good responders* showed a "mean urine sugar" under 0·25% and a fasting blood-sugar under 150 mg. per 100 ml. on tolbutamide but not on placebo. Single exceptions in either urine or blood standards did not disqualify provided that these criteria were fulfilled in the other tolbutamide period or periods.

2. *Fair responders* were obviously better controlled on tolbutamide than on placebo tablets but did not fulfil the criteria of group 1.

3. *Non-responders* did not respond to tolbutamide but never became ketotic.

4. *Potential ketotics* showed ketosis (on ferric chloride test) at any phase: these always proved non-responders.

Follow-up

After this initial assessment, patients who showed any response to tolbutamide were continued on the tablets, and they have been observed for about a year. Poor responders were usually advised to return to insulin, but many would not agree to this for some time: they constitute group 2.

Dosage of tolbutamide has varied between 1 and 4 g. daily, but has been mostly at a standard 0·5 g. four times a day. Poor responders have all been tried on 4 g. a day. Hospital attendance was at first fortnightly, and thereafter about monthly:

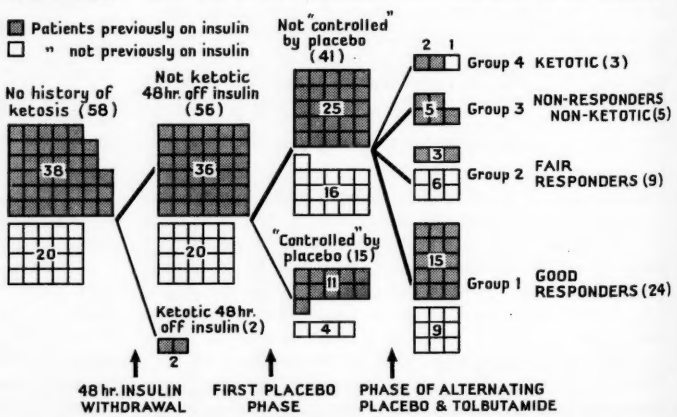

Patients previously on insulin
" not previously on insulin
No history of ketosis (58)
Not ketotic 48hr. off insulin (56)
Not "controlled" by placebo (41)
Ketotic 48 hr. off insulin (2)
"Controlled" by placebo (15)
Group 4 KETOTIC (3)
Group 3 NON-RESPONDERS NON-KETOTIC (5)
Group 2 FAIR RESPONDERS (9)
Group 1 GOOD RESPONDERS (24)
48 hr. INSULIN WITHDRAWAL
FIRST PLACEBO PHASE
PHASE OF ALTERNATING PLACEBO & TOLBUTAMIDE

Fig. 1—Results of an eight-week clinical trial of 58 apparently non-ketotic diabetics.

* Present address: Department of Medicine, King's College, Newcastle upon Tyne, 1.

urine and fasting blood-sugar were then tested. At about six-monthly intervals placebo periods were similarly recorded to check on the continuing need for tolbutamide. We could thus assess how accurately long-term responsiveness could be forecast from the initial trial.

Results

The Initial Trial

From the 58 patients who were apparently non-ketotic and uncontrollable by diet alone, the placebo phase of the trial revealed 15 as controllable by more careful diet alone; yet 11 of them had been on insulin. At various stages during the trial another 5 were found to be potentially ketotic, and so would now be placed on insulin. (In fact we did test the response of 10 patients found to be potentially ketotic: none showed any response.) We had no case of severe uncontrolled diabetes.

Of the 38 non-ketotic diabetics who entered the trial proper, 24 showed a good response to tolbutamide, 9 a fair response, and 5 no response (fig. 1.) Assuming that these 38 patients were representative of the mild diabetics at our clinic (as they should be), this would mean that about 8% of our clinic can be controlled by tolbutamide.

Persistence of Response

Fig. 2 summarises the degree of control achieved in the four groups of patients during a year's therapy: it is seen that the initial response persisted.

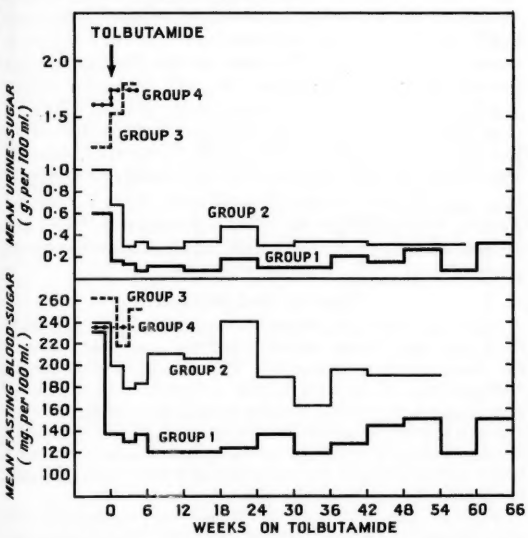


Fig. 2—Persistence of tolbutamide control. The pre-tolbutamide figures were obtained on placebo.

In 3 patients (2 of group 1 and 1 of group 2) the response was lost for no obvious reason, after three, six, and five months of tolbutamide; and 1 of the group-1 patients who lost a stone in weight during this period was later found to remain controlled in placebo. All the other patients of group 1, however, continued well on tolbutamide and lapsed on placebo (fig. 3). About 90% of patients had one or more observations in each period. The fair responders of group 2 showed on a similar chart a persistently different response to tolbutamide and placebo.

When patients of either group 2 or group 3 were returned to insulin control the original dosage still sufficed, and they tended to feel better.

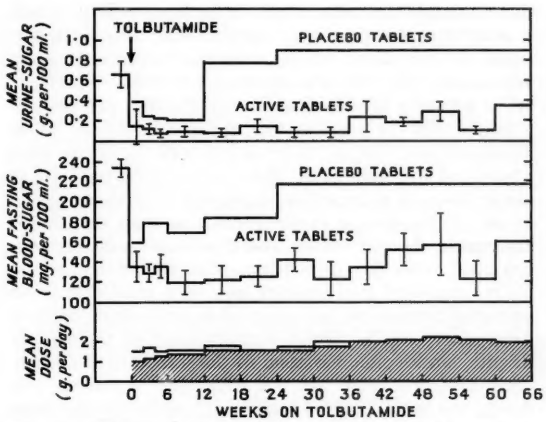


Fig. 3—Persistence of tolbutamide control and placebo relapse in the good initial responders.

One standard error of the mean for the group for each period on active tablets is shown above and below the means. The mean urine and blood-sugar values on tolbutamide remain well below the corresponding values for placebo checks. The separation of those lines indicates the continued dependence on tolbutamide. The mean dose of sulphanylurea is shown below, the clear area representing carbutamide and the hatched area tolbutamide.

The 2 group-1 patients who showed a delayed lapse of responsiveness were not obese, had not shown ketosis at any stage, had been diabetics only since the age of 50, and had been on 10–20 units of insulin. Their data are omitted from figs. 2 and 3.

Initially they responded very well to tolbutamide; but at the time of their lapse they lost about half a stone in weight, felt vaguely unwell, and failed to respond to the higher daily dosage of 4 g. tolbutamide. Tests on the first case are described by Vallance-Owen et al. (1959), which pointed to pancreatic exhaustion.

The 3rd patient, who lapsed at the twentieth week of therapy, had been a fair responder (group 2). She was 71, and her diabetes had been discovered just before she started on the tablets.

Predictability of Groups on Clinical Examination

Our findings in groups 1, 2, and 3 were checked against possible clinical indications which might serve to replace the therapeutic trial.

Age at the onset did not distinguish between the three groups; indeed, in 3 of the 24 good responders (group 1) the onset was before the age of 35. Similarly, obesity at the onset was only slightly commoner in group 1 than in groups 2 or 3; and many good responders were thin. The initial placebo fasting blood-sugars tended to be lower in groups 1 and 2 than in group 3 (group mean fasting blood-sugar 232, 240, and 262 mg. per 100 ml. respectively); but it did not distinguish group-1 from group-2 patients. The initial placebo urine tests showed that the mean figures for the groups increased as control became poorer; but there was considerable overlap of individual cases.

In short, there were no simple clinical criteria which could replace the need for a careful preliminary therapeutic trial.

Discussion

Our results agree with the findings of many others—that ketosis is a clear contraindication to tolbutamide, and that among mild diabetics who are not controlled by

diet no simple clinical criteria will distinguish the good and unsatisfactory responders. Patients who are elderly or obese at the onset of their diabetes are often good responders, but they are not the only ones. Similarly, while a fasting blood-sugar of over 250 mg. per 100 ml. suggests that the response will be poor or nil, the lower values are not confined to good responders. Initial urine sugars are also unhelpful. Acute tests of the response to single doses of tolbutamide, discussed by Vallance-Owen et al. (1959), give a better prediction than the simple fasting blood-sugar but are also unreliable in distinguishing good from fair responders. On the other hand, a short outpatient trial appears to give a good separation into good responders, fair responders, and non responders —responses which remain characteristic of the patient despite considerable variation in the tolbutamide dosage. This trial procedure has the advantage of picking out during the initial placebo phase many diabetics who were not previously achieving the best possible control by diet alone. Hence, among those previously on insulin many did not require even tolbutamide. Being an outpatient procedure, our trial assesses the degree of control which the tolbutamide can achieve, not merely whether it can alter the patient's diabetes. Tolbutamide should be given to all good responders, but not to the fair responders. The latter group require insulin even though tolbutamide may slightly improve their control.

Summary

An outpatient trial is described for choosing diabetic patients suitable for control by tolbutamide.

Response to treatment is assessed from twenty-one home urine tests and one fasting blood-sugar test performed during two fortnightly periods on placebo tablets and two on tolbutamide.

The placebo periods reveal the efficacy of diet alone; and the other periods whether tolbutamide can give a good, fair, or no response.

Tolbutamide is indicated only in good responders.

Throughout a year of subsequent therapy with tolbutamide, the same response was maintained in 21 out of 24 good responders, and in 8 out of 9 fair responders. It was little influenced by changes in dosage.

We are indebted to Dr. I. D. P. Wootton of the department of chemical pathology for the numerous blood-sugar estimations; and to Miss Allen and her pharmaceutical department. We are grateful for clinical assistance, and for generous supplies of tolbutamide and placebo tablets from Dr. F. Wolffe of the Wellcome Foundation.

REFERENCES

American Diabetes Association (1957) *J. Amer. med. Ass.* **164**, 1151.
Huggett, A. St. G., Nixon, D. A. (1957) *Lancet*, ii, 368.
King, E. J., Wootton, I. D. P. (1956) Micro-Analysis in Medical Biochemistry; p. 25. London.
Vallance-Owen, J., Joplin, G. F., Fraser, R. (1959) *Lancet*, ii, 584.

"... If my view is sound there can be no short cut to understanding science. Its theoretical terms are not simply a list of labels, except to the non-scientist. To the scientist they are summations of his scientific experience, not substitutes for it ... It is because his theoretical terms are not merely labels that the scientist finds it difficult not to use what is unkindly called jargon. The implication here is that jargon is a pretentious and unnecessary excrescence on plain words. It is not. The scientist trying to make new and publicly observable discriminations has to coin new words, because these are the only means by which the new discriminations can be precisely and publicly made and repeated by others."—B. C. BROOKES, *Listener*, Oct. 1, 1959, p. 519.

TOLBUTAMIDE CONTROL OF DIABETES MELLITUS

CLINICAL RESPONSIVENESS AND INSULIN RESERVE

J. VALLANCE-OWEN *
M.D., M.A. Cantab., M.R.C.P.
LATE MEDICAL TUTOR

G. F. JOPLIN
M.B. N.Z., M.R.C.P.
MEDICAL TUTOR

RUSSELL FRASER
M.D. N.Z., F.R.C.P.
PROFESSOR OF CLINICAL ENDOCRINOLOGY

POSTGRADUATE MEDICAL SCHOOL OF LONDON, W.12

ON many of the patients who underwent the clinical trial described by Joplin et al. (1959) we performed acute tolbutamide tests. After an overnight fast we estimated their blood-sugar and plasma-insulin activity before and two and a half hours after tolbutamide 2 g. orally. The results of these tests correlated well with whether or not the patients responded at all to the clinical trial, but they gave only a poor prediction of the long-term response. They are reported, however, because they revealed increased plasma-insulin activity after tolbutamide whenever the drug caused more than a minimal drop in blood-sugar. This increase was proportional to the fall in blood-sugar.

These results support Loubatières' original hypothesis (1944, 1957), that the sulphonylureas lower the blood-sugar by stimulating endogenous insulin production. His demonstration that the drugs can only lower the blood-sugar in animals with functioning pancreatic beta-cells has been amply confirmed (e.g., Houssay and Penhos 1956); but his hypothesis has not been finally accepted because these drugs do not reproduce all the metabolic effects of large injections of insulin (Purnell et al. 1956, Recant and Fischer 1957, Craig et al. 1958, Stowers et al. 1958) and because of earlier negative results of plasma-insulin assays (Renold et al. 1957, Weaver et al. 1958).

Material and Method

Acute tests were performed on 5 normal subjects and on 17 mild diabetics; 5 more diabetics had the acute test with only the blood-sugar estimations. The long-term tolbutamide responsiveness of the diabetics was also assessed by the clinical trial (Joplin et al. 1959). Patients already on tolbutamide were changed to placebo tablets for thirteen or more days before the acute tolbutamide test, with the exception of 2 cases who were tested after three days. Those on insulin were tested forty-eight hours after the last dose of insulin.

Most of the tests were performed on outpatients, who attended, after a twelve-hour fast, at 9 A.M. Venous blood was withdrawn; tolbutamide 2 g. was given orally; and, after two and a half hours, a second venous sample was collected. The blood-sugar in duplicate or triplicate (King and Wootton 1956) and plasma-insulin activity by the rat-diaphragm method (Vallance-Owen and Hurlock 1954, 1955) were then estimated simultaneously. The bioassay of plasma-insulin activity was performed and recorded by one of us (J. V.-O.) in ignorance of the clinical response, 3 of the cases being tested before entering the clinical trial.

Results

Plasma-insulin Activity

Fig. 1 gives the results of the plasma-insulin-activity assays in normal subjects, responsive diabetics, and unresponsive diabetics (as determined by clinical trial).

* Present address: Department of Medicine, King's College, Newcastle upon Tyne, 1.

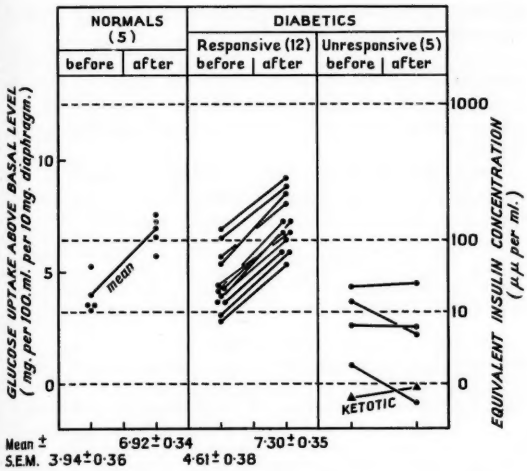


Fig. 1—Plasma-insulin activity before and two and a half hours after tolbutamide 2 g.

The results in responsive diabetics approximate closely to the results in normals in both fasting levels and the rise after tolbutamide. However, the 7 good clinical responders gave similar values to the 5 fair responders. While the unresponsive diabetics may have only slightly lower fasting levels, they differ sharply from the other two groups in showing no rise in plasma-insulin activity after tolbutamide.

Blood-sugar Response

With the subjects grouped as before, fig. 2 shows the fall in blood-sugar after tolbutamide, expressed as a percentage of the fasting level. Again the normal response

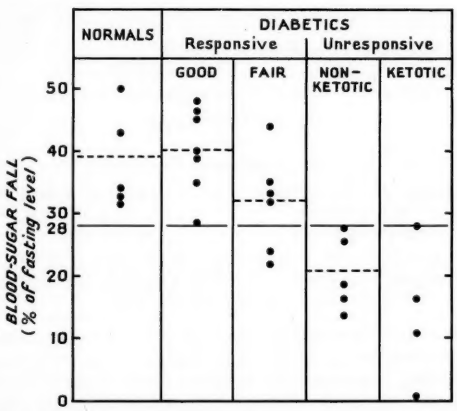


Fig. 2—Fall in blood-sugar two and a half hours after tolbutamide 2 g. The mean for each group is marked.

is reproduced by responsive diabetics, in contrast to the minimal fall in non-responding ones. Of the 12 cases showing less than a 28% fall, 9 were in the clinically unresponsive group and 2 had shown only a poor clinical or long-term response to tolbutamide.

Correlation between Blood-sugar Response and Plasma-insulin Activity

Fig. 3 shows a close correlation between these two effects of tolbutamide. (For normals and responsive diabetics $r=0{\cdot}69$; $P<0{\cdot}01$.)

Serial Tests on an Initially Responsive Diabetic

A 55-year-old diabetic, previously stabilised on 20 units of insulin per day, achieved good diabetic control during a few months on tolbutamide therapy, 0·5 g. twice daily. After twenty-four weeks control was completely lost, even after raising the dose to 1·0 g. four times daily. However, she would not discontinue tolbutamide until six months later. At this stage, and before resuming insulin, the acute tolbutamide test showed non-responsiveness. Good diabetic control was then achieved with the same dose of insulin as originally; and, after another six months, a second acute tolbutamide test again showed a good response. This implied a recovery of pancreatic reserve (see table).

Discussion

Plasma-insulin activity rose following a dose of tolbutamide in normal subjects and in those mild diabetics

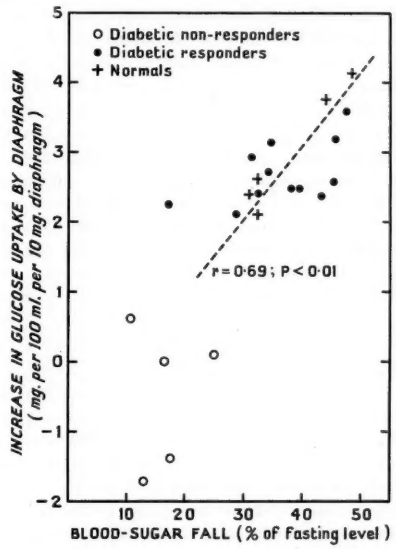

o Diabetic non-responders
• Diabetic responders
+ Normals
r=0·69; P<0·01
INCREASE IN GLUCOSE UPTAKE BY DIAPHRAGM (mg. per 100 ml. per 10 mg. diaphragm)
BLOOD-SUGAR FALL (% of fasting level)

Fig. 3—Fall in blood-sugar and rise in plasma-insulin activity two and a half hours after tolbutamide 2g.

who showed some response clinically to the drug, whereas no such rise occurred in diabetics who were clinically unresponsive. The rise in plasma-insulin activity, moreover, correlated well with the fall in blood-sugar. This is strong evidence that in man tolbutamide lowers blood-sugar by stimulating insulin secretion. (Animal experiments leave no room for doubt that it stimulates the production of insulin by the beta-cells [Pfeiffer et al. 1958].) Tolbutamide may, of course, have other effects

ACUTE TOLBUTAMIDE—RESPONSE TESTS ON AN INITIALLY GOOD RESPONDER IN WHOM CONTROL WAS LOST AFTER TWENTY-FOUR WEEKS' THERAPY

—	Plasma-insulin activity (increase in glucose uptake in mg. per 100 ml. plasma per 10 mg. diaphragm)			Blood-sugar (mg./100 ml.)		
	Fasting	2½ hr. after tolbutamide 2 g.	Change	Fasting	2½ hr. after tolbutamide 2 g.	% fall
After 63 weeks' tolbutamide (3 days since last dose)	3·7	2·3	−1·4	392	320	18%
After 6 months' insulin (48 hours since last dose)	3·2	5·9	+2·7	235	156	34%

as well; but its effect on insulin production alone could explain all its known actions.

Tolbutamide itself neither increases the glucose uptake of the diaphragms used in the insulin assay, nor enhances the effect of standard insulin solutions (Fry and Wright 1957, 1958, Vallance-Owen unpublished).

Hitherto this pancreatic-stimulation hypothesis has seemed inadequate, particularly because many investigators have failed to show an increased peripheral utilisation of glucose or a rise in plasma-insulin activity when the drug lowers blood-sugar. However, a fall in blood-sugar, the peripheral utilisation remaining unchanged, is in fact an insulin-like effect. Recently Butterfield et al. (1958) have shown that both tolbutamide and insulin lower the "threshold" arterial glucose concentration at which glucose can enter the cells; and Jacobs et al. (1958) have shown that small subcutaneous injections of insulin have effects similar to those of tolbutamide—they lower the hepatic output of glucose without changing its peripheral utilisation. Mild diabetics who respond to tolbutamide are probably "compensated": their peripheral utilisation of glucose may be normal, probably as a result of their raised blood-sugar. Hence the small increase in circulating insulin induced by tolbutamide will not alter their normal peripheral utilisation of glucose but will rather enable this to occur at a lower blood-sugar level. A large increase in insulin output would no doubt entail an increase in peripheral utilisation.

The failure of other workers to show a rise in plasma-insulin activity after tolbutamide can also be explained. Weaver et al. (1958), though they used the rat-diaphragm technique, achieved only a relatively insensitive assay; their lowest standard insulin concentration was 2500 microunits per ml. Their negative results are thus not surprising. Renold et al. (1957), using the same technique, were able to measure down to 100 microunits per ml.; but our findings suggest that mean values for plasma-insulin activity after tolbutamide in normal subjects or responsive diabetics do not greatly exceed 100 microunits per ml. (fig. 1). These investigators, moreover, worked under different conditions from ours: they sampled bloods between ten and forty minutes after the rapid intravenous injection of tolbutamide, whereas we gave the drug orally and studied the effect only two and half hours later.

Our results confirm that single-dose tolbutamide tests give only an approximate prediction of the drug's long-term clinical control (Marble 1958). They can distinguish between unresponsive diabetics and most of those who will show some persistent response; but they do not distinguish between patients who will be satisfactorily controlled and those whose control will be only fair. The difference between these good and fair responders probably depends on the adequacy of their insulin reserves. When the reserve is small, a single tolbutamide dose may well cause an impressive response, but a larger reserve is doubtless required for a sustained response to regular daily stimulation. In only a few of our patients did the response become exhausted on continued administration of the drug (Pfeiffer et al. 1957)—another reason for confining its use to patients who can be adequately controlled during a clinical trial.

Summary

The blood-sugar and plasma-insulin activity before and two and a half hours after tolbutamide 2 g. have been measured in 5 normal subjects and 22 diabetics. The diabetics were also independently graded in their clinical responsiveness to tolbutamide.

In this acute test the plasma-insulin activity rose in normals and in the clinically responsive diabetics but not in the clinically unresponsive diabetics. The fall in blood-sugar correlated ($r=0{\cdot}69$) with this rise in plasma-insulin activity.

These results suggest that tolbutamide lowers blood-sugar by stimulating endogenous insulin production, when there is an adequate pancreatic insulin reserve.

We are indebted to Miss E. Dennes, working on a Medical Research Council grant, for technical assistance with the plasma-insulin assays; and to Mrs. K. Vartan, working on a grant from the British Insulin Manufacturers, for the blood-sugar estimations.

REFERENCES

Butterfield, W. J. H., Fry, I. K., Holling, H. E. (1958) *Diabetes*, **7**, 449.
Craig, J. W., Molzahn, V. J., Woodward, H., Miller, M. (1958) *ibid.* p. 267.
Houssay, B. A., Penhos, J. C. (1956) *Metabolism*, **5**, 727.
Jacobs, G., Reichard, G., Goodman, E. H., Friedman, B., Weinhouse, S. (1958) *Diabetes*, **7**, 358.
Joplin, G. F., Fraser, R., Vallance-Owen, J. (1959) *Lancet*, ii, 582.
Fry, I. K., Wright, P. H. (1957) *Brit. J. Pharmacol.* **12**, 350.
— — (1958) Personal communication.
King, E. J., Wootton, I. D. P. (1956) Micro-analysis in Clinical Biochemistry; p. 25. London.
Loubatières, A. (1944) *C.R. Soc. biol. Paris*, **138**, 766.
— (1957) *Ann. N.Y. Acad. Sci.* **71**, 192.
Marble, A. (1958) *Med. Clin. N. Amer.* September, p. 1163.
Pfeiffer, E. F., Renold, A. E., Martin, D. B., Dagenais, Y., Meakin, J. W., Nelson, D. H., Schoemaker, G., Thorn, G. W. (1958) Communication 75. International Diabetic Federation Congress, Dusseldorf.
— Schöffling, K., Steigerwald, H., Treser, G., Otto, M. (1957) *Dtsch. med. Wschr.* **82**, 1528.
Purnell, R., Arai, Y., Pratt, E., Hlad, C., Elrick, H. (1956) *Metabolism*, **5**, 778.
Recant, L., Fischer, G. L. (1957) *Ann. N.Y. Acad. Sci.* **71**, 62.
Renold, A. E., Martin, D. B., Boshell, B. R., Thorn, G. W. (1957) *ibid.* p. 71.
Stowers, J. M., Mahler, R. F., Hunter, R. B. (1958) *Lancet*, i, 278.
Vallance-Owen, J., Hurlock, B. (1954) *ibid.* i, 68.
— — Please, N. W. (1955) *ibid.* ii, 583.
Weaver, J. A., Prout, T. E., Scott, G. W., Asper, S. P. (1958) *Brit. med. J.* i, 425.

POLIOMYELITIS-VIRUS FLOCCULATION REACTION

Behaviour of Sera of Cases and Vaccinated Individuals*

WILSON SMITH
M.D. Manc., F.R.C.P., F.R.S.
PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF LONDON

G. P. B. BOISSARD
B.Sc., M.B. Lond.
OF THE VIRUS REFERENCE LABORATORY

GILLIAN M. CHURCHER
M.B. Lond.
RESEARCH ASSOCIATE

LESLEY PARKER
B.Sc. W. Aust.
RESEARCH ASSOCIATE

From the Department of Bacteriology, University College Hospital Medical School, London, W.C.1, and the Virus Reference Laboratory, P.H.L.S., Colindale, London, N.W.9

IN a previous communication a direct flocculation reaction between poliomyelitis viruses of the three major types and type-specific immune sera was described (Smith et al. 1956a). The flocculating antigens used were highly concentrated and partially purified suspensions of the viruses grown in cell cultures, and the type specificity of the reaction was established by means of type-specific immune sera, obtained by the artificial immunisation of rabbits. It was also shown, however, that some human sera from paralytic cases of poliomyelitis produced virus flocculation. Indeed attention was drawn to the potential value of the reaction as a means of early and rapid diagnosis, but we pointed out that, for a serological survey, a simpler method of antigen production was desirable and a modification of the original flocculation test was required to allow the examination of small samples of sera.

* Aided by a grant from The National Foundation.

The successful solution of these problems has already been reported (Smith et al. 1956b, Churcher et al. 1959) and the present report concerns the examination of sera of poliomyelitis cases and of individuals immunised with Salk vaccine. An attempt has also been made to correlate the flocculation results with data of complement-fixing and virus-neutralising potencies.

Materials and Methods

Virus Antigens

Batches of antigens of each virus type were made from virus culture fluids obtained from three sources: our own laboratory; the M.R.C. Virus Laboratory, Carshalton; and the Virology Unit, M.R.E., Porton. Each laboratory used the same virus strains (Brunhilde type 1, MEF 1, type 2, and Leon type 3) and the same line of transformed rabbit kidney cells (ERK) originally isolated by Westwood et al. (1957). In this laboratory virus propagation was in monolayer cell cultures in babies feeding-bottles; in both the outside laboratories it was in suspensions of the ERK cells.

All virus fluids were clarified by horizontal centrifugation at approximately 1800 r.p.m. for 15 min. and then filtered through Seitz pads. They were then matched against a provisional standard antigen by a simple line flocculation test with twofold serial dilutions of the antigens against a 1 in 15 dilution of a standard rabbit antiserum. Those giving approximately the same end-point as the standard antigen were used without further processing; otherwise they were centrifuged in the 'Spinco' at 30,000 r.p.m. for $2^1/_2$ hr., and the virus deposit was resuspended in an appropriate volume of saline solution. Though crude, this method of antigen standardisation was found to be adequate for our purposes.

The antigens were stored frozen at −10°C until required. When thawed some of them contained small aggregates visible either by naked eye or microscopically, in which case they were reclarified by centrifugation at 1800 r.p.m. for 10 min. This removal of aggregates was shown to be without any detectable effect on flocculation potency.

Rabbit Antisera

These were obtained as described previously (Smith et al. 1956a). For each type, a pool of sera from different rabbits and from successive bleeds was made, dispensed in 1 ml. quantities in vials and stored frozen at −10°C.

Human Sera

Two categories of human sera were investigated—"case" sera and "vaccination" sera. Paired samples, "acute" and "convalescent", of 41 poliomyelitis cases were obtained from several sources. Of the acute samples 30 were obtained during the first week of illness and 8 during the second week; for the remaining 3, the day of bleeding was not ascertained. All convalescent samples were taken in the period from the beginning of the third week to the end of the fifth week after onset. The serum donors included both paralytic and nonparalytic cases, but the clinical information available was not sufficient for any analysis of results on the basis of severity of illness. It should be emphasised, however, that a type-1 poliomyelitis virus was isolated from every one of the 41 cases.

Pre- and post-vaccination sera of 50 individuals were examined. All of the donors received two doses of Salk vaccine with an interval of four to five weeks between doses, and the second serum sample was taken from two to three weeks after the second dose. A few of these were found to be originally triple-negative by the virus neutralisation test; these were given a booster dose of vaccine from seven to twelve months later and further serum samples were obtained just before, and from two to three weeks after, the booster inoculation.

Flocculation Test

The microflocculation method described by Smith et al. (1956b) was used. Briefly this consists of mixing 0·02 ml. quantities of the virus antigens and dilutions of sera in Dreyer agglutination tubes, incubating the mixtures at 37°C in a humidity box for four hours, and then examining a hanging-drop preparation of each mixture by low-power dark-ground microscopy. Although we found that flocculation could be detected by ordinary light or by phase-contrast microscopy we decided to retain the dark-ground method because we considered it more sensitive for the detection of very weak reactions, especially those given by vaccination sera, in which the floccules are often of very fine granular type.

All the case sera and most of the vaccination sera were tested over a range of fivefold dilutions, from 1 in 1 (undiluted) to 1 in 125, against a constant dose of the undiluted antigen of each virus type. With some of the vaccination sera the sample available was so small that they could only be tested at the three fivefold dilution levels.

Positive controls of the antigens with homologous rabbit antisera and negative controls of antigens and sera with saline were included in every test.

This simple test is quite inadequate for antibody titration and was designed for the detection of flocculating antibodies at any level with only a rough indication of the relative potencies of different sera.

Complement-fixation Tests

The method of Fulton and Dumbell (1949) was used in straight-line tests (Le Bouvier 1953). Antigens were virus fluids from cultures of the strains Mahoney, MEF 1 and Saukett. The viruses were grown in monolayer cultures of monkey-kidney cells maintained in medium 199 (Morgan et al. 1950) without added serum. The living virus antigens were used at optimal concentration, as determined by chessboard titrations with a type-1 human convalescent serum and hyperimmune rhesus-monkey sera specific for each type. The test sera were diluted 1 in 4 in barbitone buffer and inactivated at 60°C for 20 min.; twofold dilutions to 1 in 64 dilution were tested. A constant dose, 2 HD_{50}, of guineapig complement was used. Controls in each test comprised test sera at each dilution, antigens, virus culture medium, sheep red cells, and human type-1 convalescent serum. Fixation titres were expressed as reciprocals of the dilutions of the sera in buffer saline at the 50% hæmolysis end-point.

Virus Neutralisation

The sera of vaccinated persons were titrated at the M.R.C. Biological Standards Laboratory, Hampstead, and the figures kindly placed at our disposal for correlation with our flocculation results.

Results

Flocculation Behaviour of "Case" Sera

Analyses of the results obtained with acute and convalescent serum samples of 41 poliomyelitis cases are given in tables I–III. It should be emphasised that a type-1 virus was isolated from the fæces of every case. Type-2 and type-3 cases are not included in the present report because the numbers investigated so far are too small for analysis, but such information as is available indicates that conclusions to be drawn from the type-1 series will be generally applicable to all types. The type-1 cases included both paralytic and non-paralytic infections, but clinical information was not sufficient for their separation into the two categories.

Figures in the tables show the numbers of sera which gave flocculation at a dilution 1 in 5 or higher, and complement-fixation at 1 in 8 or higher. Any diagnostic significance of positive reactions obviously depends on the behaviour of sera of normal healthy individuals, and

TABLE I—CORRELATION OF FLOCCULATION AND COMPLEMENT-FIXATION REACTIONS OF PAIRED SERA OF 41 CASES OF TYPE-1 POLIOMYELITIS

Antigen	Flocculation +		Complement fixation +	
	Acute	Conv.	Acute	Conv.
Type 1 ..	33 (*80%*)	30 (*73%*)	21 (*51%*)	36 (*88%*)
„ 2 ..	12 (*30%*)	13 (*32%*)	7 (*17%*)	7 (*17%*)
„ 3 ..	22 (*54%*)	20 (*49%*)	16 (*39%*)	16 (*39%*)

TABLE II—CHANGES OF ANTIBODY LEVELS DURING CONVALESCENCE IN 41 CASES OF TYPE-1 POLIOMYELITIS

Antibody level	Type 1		Type 2		Type 3	
	Floccu-lation	Com-plement fixation	Floccu-lation	Com-plement fixation	Floccu-lation	Com-plement fixation
Rise ..	5 (12%)	22 (54%)	3	4	5	5
Fall ..	11 (27%)	5 (12%)	8	1	7	3
No change	25 (61%)	14 (34%)	30	36	29	33

it was found that about 28% of these gave some degree of type-1 flocculation when tested undiluted. Tested at the 1 in 5 dilution level, however, only 6% flocculated. It was therefore decided to score as positive reactions only those occurring at 1 in 5, or greater, serum dilution, and similarly with complement fixation only those at 1 in 8 or greater.

On this basis it will be seen from table I that 80% of acute sera and 73% of convalescent sera gave type-1 flocculation reactions, compared with 51% and 88% respectively giving complement fixation. This in itself suggests that qualitatively different type-specific antibodies may be concerned in the two reactions and that any particular advantage the flocculation test may have as a means of diagnosis is likely to be in the early acute stage of infection. This is supported by the data in table II. The great majority of cases show either a fall or no change of flocculating antibody level during early convalescence, whereas 54% show a rise of C.F. antibodies. It may be significant that three of the four serum samples which were collected within 48 hr. of onset of illness gave strong flocculation at 1 in 25 dilution, and that no samples collected at any stage reacted at 1 in 125 dilution. Such early appearance of antibodies, followed by early decline, presents a most unusual picture of serological response to infection meriting further investigation; for an early decline to a very low level may be an important factor in diagnostic application of the reaction.

Both the flocculation and C.F. tests gave heterotypic reactions with many sera, both acute and convalescent. They occurred much more frequently in the flocculation test, but, with both tests, only about half as many sera gave type-2 reactions as those giving type-3 reactions. As in the case of homotypic antibodies, heterotypic-antibody levels may rise or fall during convalescence, but with most serum pairs no change of level was apparent. Table III gives the frequencies with which the various combinations of homotypic and heterotypic reactions were encountered. Usually, but not invariably, the homotypic titre was higher than the heterotypic titre. The analysis also shows that some sera reacted with type-2 or type-3 antigen, or with both, whilst failing to react with type-1 antigen and that others were triple negative. Possible explanations of these various anomalies

TABLE III—HETEROLOGOUS REACTIONS OF SERA FROM 41 TYPE-1 POLIOMYELITIS CASES

Reactions with antigen	Flocculation			Complement fixation		
	Acute	Conv.	All samples	Acute	Conv.	All samples
Type 1 only ..	11	12	23	8	20	28
„ 2 „ ..	0	0	0	1	1	2
„ 3 „ ..	2	2	4	2	0	2
„ 1+2 ..	2	1	3	1	0	1
„ 1+3 ..	11	6	17	9	10	19
„ 1+2+3	9	11	20	3	6	9
„ 2+3 ..	1	1	2	2	0	2
Triple −ve ..	5	8	13	15	4	19
Totals ..	41	41	82	41	41	82

are: infections with more than one virus type, infections with viruses other than poliomyelitis, and anamnestic reactions based on previous non-clinical infections with the heterologous virus types.

Flocculation Behaviour of "Vaccination" Sera

The paired sera, pre- and post-vaccination, of 50 persons receiving two doses of trivalent vaccine were investigated. In this series complement-fixation tests were not done but all the samples were titrated for virus-neutralising antibodies to the three virus types at the M.R.C. Biological Standards Laboratory. As the lowest serum dilution tested was 1 in 8 for more than half the sera, neutralisation activity was scored as positive only if present at this dilution or higher. In the flocculation tests, reactions at 1 in 5 or higher serum dilutions were scored as positive.

The total numbers of positive sera in each group are given in table IV. The pre-vaccination sera represent, of course, a sample of the normal population; and of these 50, 61, and 74% had neutralising antibodies to types 1, 2, and 3 viruses respectively. This contrasts with 6, 10, and 14% with flocculating antibodies. Vaccination resulted in the presence of neutralising antibodies in

TABLE IV—CORRELATION OF FLOCCULATION AND VIRUS-NEUTRALISATION REACTIONS OF 50 PAIRED SERA FROM INDIVIDUALS IMMUNISED WITH 2 DOSES OF SALK VACCINE

Sera	Antigen types	Flocculation		Virus neutralisation	
		+	−	+	−
Pre-vacc. ..	1	3	47	25	25
	2	5	45	30	19*
	3	7	43	37	13
Post-vacc. ..	1	24	26	48	2
	2	22	28	48	0*
	3	21	29	49	1

* 3 samples were not tested for type-2 virus neutralisation.

almost 100% of donors, irrespective of their pre-vaccination status, but converted rather less than 50% to flocculation reactors. This difference may be largely due to the time of post-vaccination sampling—usually two to three weeks after the second vaccine dose. In view of the very early appearance and early decline of flocculating antibodies in type-1 poliomyelitis cases, it is possible that post-vaccination sera obtained within three or four days of the second inoculation might give a completely different picture. It is also possible that sampling after an interval of a few months would fail to reveal any significant effect of vaccination on flocculating antibody production. For a full assessment of the diagnostic potentialities of the reaction further investigations along these lines are essential.

In table V an attempt has been made to correlate flocculation activity with levels of neutralisation antibodies selected arbitrarily as low (titres less than 64), medium (titres 64–1024), and high (titres greater than 1024). No positive correlation was shown by pre-vaccination sera; but post-vaccination sera, and hence all the samples taken together, showed a rough correlation of flocculation activity with high neutralisation-antibody titres. Nevertheless the fact that some sera with very low neutralisation titres flocculate with the corresponding antigen type and that, conversely, 40–60% of those with very high neutralisation titres fail to flocculate, reinforces the conclusion drawn from the case serum results that at least two qualitatively different kinds of antibody are concerned in the different types of serological reactions.

TABLE V—CORRELATION OF FLOCCULATION REACTIVITY AND LEVELS OF NEUTRALISING ANTIBODIES IN PAIRED SERA OF 50 VACCINATED INDIVIDUALS

Sera	Antigen type	Neutralising-antibody levels			Totals
		<64	64–1024	>1024	
Pre-vacc. ..	1	0/30	2/15	1/5	3/50
	2	3/31	1/10	1/8	5/49*
	3	6/24	1/22	0/4	7/50
Post-vacc. ..	1	1/12	8/16	15/22	24/50
	2	3/8	9/22	10/18	22/48*
	3	0/7	5/11	16/32	21/50
All samples	1	1/42	10/31	16/27	27/100
	2	6/39	10/32	11/26	27/97*
	3	6/31	6/33	16/36	28/100

Numerators = numbers of sera giving + flocc.
Denominators = numbers of sera in each neutralisation category.
* 3 samples were not tested for type-2 virus neutralisation.

Of the 50 vaccinated persons 9 were originally triple-negative by both flocculation and virus-neutralisation tests. After two doses of vaccine their sera still failed to flocculate, even undiluted, and their neutralisation titres were low. They were therefore given a third, booster, dose of vaccine nine to twelve months later and were bled two to three weeks after this booster dose. From 9 other persons, originally found to be triple-negative, only post-booster sera were available for flocculation tests. The results obtained with this series are shown in detail in table VI; the number of samples is too small for analysis of the kind adopted for the two-dose vaccination series.

Neutralisation antibody responses for types 2 and 3 viruses were extremely good; for each type, 14 sera fall into the high antibody range and 4 sera into the medium range. Type-1 responses were much more variable and on the whole much poorer. The percentages of sera giving flocculation were not significantly different from those in the two vaccine dose series. This is in line with the generally accepted conclusion that responses of triple-negative persons to a third dose of vaccine are similar to those of persons with some basic immunity to two doses. The figures in the table strikingly illustrate the dissociation between neutralising-antibody titre and flocculating activity, for both extremely high and extremely low titres are associated with both presence and absence of flocculating antibodies. The results, however, reveal a curious phenomenon which occurred much less frequently with the post-vaccination sera of the two-dose series. This is that, with 3 exceptions, all the sera either failed to flocculate with any antigen type or did so with all three types, quite irrespective of their neutralisation titres. Thus 8 of the 11 flocculating sera were triple-positive although type-1 neutralising antibodies were undetectable in 2 and 2 others had type-1 titres of 16 and 32. On the other hand 5 of the 7 triple-negative sera had high or moderately high neutralisation titres against all three virus types. Whatever may be the factor responsible for the relatively poor type-1 neutralising-antibody responses to the third booster dose of vaccine, it was clearly not operative in determining the flocculating-antibody response.

TABLE VI—FLOCCULATION AND VIRUS-NEUTRALISATION TITRES OF ORIGINALLY TRIPLE-NEGATIVE INDIVIDUALS AFTER A THIRD, BOOSTER, INOCULATION OF TRIVALENT VACCINE

Flocculation titres			Neutralisation titres		
1	2	3	1	2	3
0	0	0	4096	8192	4096
0	0	0	128	4096	8192
0	0	0	8192	8192	4096
0	0	0	64	16348	4096
0	0	0	16	2048	256
0	0	0	4096	1024	2048
0	0	0	128	4096	1024
0	0	5	512	2048	4096
0	0	5	2048	4096	8192
0	5	5	<2	512	512
5	5	5	128	16384	16384
5	5	5	2048	8192	8192
5	5	5	<4	512	2048
5	5	5	1024	4096	8192
5	5	5	32	1024	2048
5	25	5	1024	4096	4096
5	5	25	128	2048	128
25	25	25	16	2048	2048

Discussion

The results of the present investigation support the view, expressed in our earlier papers, that the direct poliomyelitis flocculation reaction may provide a very simple method for the early and rapid diagnosis of poliomyelitis-virus infections, with certain advantages not shared by the other serological tests. This conclusion, however, is subject to the qualification that the significance of a reaction obtained with the serum of a suspected case may depend upon the vaccination status of the general community. Most of our case sera were obtained before any appreciable percentage of the population had been vaccinated. Further serological surveys are therefore urgently required to determine the magnitude, and more especially the duration, of flocculating-antibody responses to vaccination. Should it be found that these decline rapidly to very low antibody levels, a strongly positive reaction within the first few days of an illness would be a very strong indication that the case was one of poliomyelitis-virus infection.

The only other report of the diagnostic significance of the flocculation reaction (Schmidt and Lennette 1959) appeared while this report was being prepared. Paired sera of 53 cases, 41 of which were type-1 infections, were investigated by a modification of our original method of micro-flocculation and were also titrated for complement-fixing and virus-neutralising antibodies. Unfortunately no sera of healthy unvaccinated and vaccinated persons were included. Their results differ from ours in several important respects. Thus Schmidt and Lennette obtained a positive flocculation reaction at 1 in 4, or higher, serum dilution with one or other of the serum samples of every patient from whom a poliomyelitis virus had been isolated. Moreover, although they, too, note the tendency for flocculating antibodies to appear earlier and decline earlier than complement-fixing antibodies, 51% of their cases showed at least a fourfold rise of titre during the illness. They therefore assess the diagnostic significance of the test solely on the basis of a fourfold antibody rise and suggest that its chief value will be as an adjunct of complement-fixation for the detection of such antibody rises. Our own results, on the contrary, indicate that the test is of little use for the detection of fivefold antibody rises and that the reactivity of very early serum samples is all-important. Indeed, if no reaction is obtained with an early sample, there would appear to be little advantage in repeating the test on a later sample, for in none of our 41 pairs was the convalescent serum positive when the acute serum was negative.

These discrepancies between the American findings and our own are difficult to understand but may be due to the differences in technique, especially in the period of incubation of virus-serum mixtures before microscopic examination; eighteen hours as against four hours. Some increase of titre almost invariably results on further incubation beyond the four-hour period which we adopted, so extension of the period to eighteen hours

would probably have led to the detection of positive reactions with many of our sera scored as negative. It is also possible that flocculating antibodies vary in speed of reaction and, if slow-reacting components appear relatively late in response to infection, the detection of significant rises of titre would demand the longer incubation period. Another unknown factor is the immunological status of the populations under investigation which is determined by the frequency of subclinical infections and vaccinations.

A further difference between the American and British results is in the frequency of heterotypic reactions. In both series these were more frequent with flocculation than with complement fixation, but the American figures of 21 and 17% contrast with approximately 50 and 38% given by our sera. Although we found that most sera giving both homotypic and heterotypic reactions had a higher homotypic titre in both flocculating and complement-fixing tests, some sera had a higher heterotypic titre in both tests. Possible reasons are infections with more than one virus type or previous subclinical infection with the heterologous type. Whatever the reason, this militates against the value of flocculation for type diagnosis.

In nearly all human infectious diseases serological diagnosis is retrospective, depending on the detection of a significant rise of specific antibodies. The possibility of diagnosis being based upon the appearance of flocculating antibodies in the earliest stages of illness, followed by their rapid decline, introduces a new concept into diagnostic serology, though how far the phenomenon may be due to previous non-clinical infection, thus representing a secondary immunological response, remains to be determined. If this is the underlying factor it is still difficult to understand why the secondary responses are not equally detectable by complement fixation and virus neutralisation. All the evidence, however, points clearly to a qualitative difference between antibodies which flocculate and those which do not, although capable of neutralising the virus. The lack of correlation between virus-neutralising titres and flocculating potency, most strikingly exemplified by the results presented in table VI, leave no escape from this conclusion. Both kinds of antibody are type-specific and both are demonstrably capable of direct combination with the virus. Whether flocculating antibodies also neutralise is not yet known. Two alternative hypotheses present themselves: (1) different antigenic components of the virus may partake in the antigenic stimulus of infection or vaccination; or (2) a single antigen may evoke the production of both monovalent and multivalent antibodies, in which case only the latter could form the virus-antibody lattices required for visible flocculation. The fact that neutralising antibodies themselves are heterogeneous, in the sense that they may have different degrees of avidity for the virus, tends to support the second hypothesis, but crucial evidence must await the separation of flocculating antibodies in a pure state, which is now being attempted. The point may well be of considerable importance for the assessment of the protective value of vaccination as distinct from its effects on neutralising-antibody titres.

The effects of vaccination in triple-negative persons are puzzling and require further investigation. From table VI it will be seen that serum samples after a third, booster, dose tended to be either triple-negative or triple-positive by the flocculation test, quite irrespective of their widely variable neutralising-antibody titres for the three virus types. Thus, of the 11 flocculating sera 8 were triple-positive, although 3 of these had extremely low neutralising-antibody titres for type-1 virus, and 2 others low titres. This, in conjunction with the frequency of heterotypic reactions with the type-1 case sera, raises the question whether a group antigen common to the three virus types is involved. Evidence for the existence of such a group antigen has been obtained by several workers (Black and Melnick 1955, Melnick 1955, Hummeler and Hamparian 1958a and b). We have never succeeded in demonstrating a group reaction by flocculation; nor could the associations of type reactions shown in table III be explained on this basis. Moreover increases in heterotypic neutralising antibody following infection are not infrequent. In the light of current immunological theory it may not be too heterodox to suggest that the stimulus of a single type-specific antigen may spread, to affect cells which have been previously conditioned to produce antibodies to the other virus types. A detailed study of the immunological responses of originally triple-negative individuals, following sequential vaccination with monovalent vaccines of the three types, might yield crucial evidence.

Evaluation of the full significance of the flocculation behaviour of sera requires further analysis of the reaction in terms of the D (intact virus) and C (degraded virus) components of virus suspensions (Schwerdt and Schaffer 1956, Le Bouvier et al. 1957, Le Bouvier 1959). The flocculation which occurs with our standard rabbit antisera is known to be the resultant of the reactions of these two distinct antigen-antibody systems. With human case sera the D system appears to be chiefly, if not wholly, involved; but how far intervention of the C system may account for some of the anomalous results, especially those obtained with vaccination sera, is not known.

Conclusions and Summary

Paired sera of 41 cases of type-1 poliomyelitis, 50 persons vaccinated with two doses of Salk vaccine, and 16 triple-negative persons, given a third, booster, dose of vaccine, were examined by the direct poliomyelitis-virus flocculation test. The case sera were also titrated for complement-fixing antibodies, and virus-neutralisation titres of all the vaccination sera were supplied to us for comparative analysis.

The results indicate that the flocculation test provides a valuable means of diagnosis, with important advantages over the other available serological tests. This test is applicable in the earliest stages of illness and does not depend upon the detection of significant rises of antibody levels during the disease. Results may be obtained within a few hours.

These conclusions are subject to the qualification that the duration of detectable flocculating antibodies evoked by vaccination is not yet known.

The immunological responses to vaccination indicate that poliomyelitis flocculating antibodies differ from virus-neutralising antibodies and that the qualitative nature of the response may depend upon the immunological status of the individual at the time of vaccination.

Expenses of the work were defrayed from grants by the National Foundation (U.S.A.) and the National Fund for Poliomyelitis Research. G. M. C. was supported by the National Fund for Poliomyelitis Research, and L. P. by a grant from the London Fever Hospital Research Fund. Thanks are due to many colleagues for their generous help. Dr. J. O'H. Tobin and his colleagues of the M.R.C. Laboratories, Hampstead, placed the virus-neutralisation data at our disposal, and also supplied many of the vaccination sera. Batches of virus culture fluids were received from Dr. J. C. N. Westwood,

M.R.E., Porton, and Dr. P. D. Cooper of the M.R.C. Virus Laboratory, Carshalton. Poliomyelitis case sera were supplied by Dr. J. A. Dudgeon, St. George's Hospital, and by Dr. Joan Davies, Dr. B. P. Marmion, Dr. A. J. H. Tomlinson, Dr. Bruce White, and Dr. Margaret Wilson, of the Public Health Laboratory Service. Collection of the sera by the regional laboratories was kindly organised by Dr. F. O. MacCallum, Virus Reference Laboratory, Colindale.

REFERENCES

Black, F. L., Melnick, J. L. (1955) *Proc. Soc. exp. Biol., N.Y.* **89**, 353.
Churcher, G. M., Sheffield, F. W., Smith, W. (1959) *Brit. J. exp. Path.* **40**, 87.
Fulton, F., Dumbell, K. R. (1949) *J. gen. Microbiol.* **3**, 97.
Hummeler, K., Hamparian, V. V. (1958a) *Fed. Proc.* **17**, 518.
— — (1958b) *J. Immunol.* **81**, 499.
Le Bouvier, G. L. (1953) *Brit. J. exp. Path.* **34**, 300.
— (1959) *ibid.* (in the press).
— Schwerdt, C. E., Schaffer, F. L. (1957) *Virology*, **4**, 590.
Melnick, J. L. (1955) *Proc. Soc. exp. Biol., N.Y.* **89**, 131.
Morgan, J. F., Morton, H. J., Parker, R. C. (1950) *ibid.* **73**, 1.
Schmidt, N. J., Lennette, E. H. (1959) *Amer. J. Hyg.* **70**, 51.
Schwerdt, C. E., Schaffer, F. L. (1956) *Virology*, **2**, 665.
Smith, W., Sheffield, F. W., Lee, L. H., Churcher, G. M. (1956a) *Lancet*, i, 710.
— — Churcher, G. M., Lee, L. H. (1956b) *ibid.* ii, 163.
Westwood, J. C. N., MacPherson, I. A., Titmuss, D. H. J. (1957) *Brit. J. exp. Path.* **38**, 138.

CHROMOSOMAL SEX IN THE SYNDROME OF TESTICULAR FEMINISATION

PATRICIA A. JACOBS
B.Sc. St. And.

A. G. BAIKIE
M.B. Glasg., M.R.C.P.E.

W. M. COURT BROWN
M.B., B.Sc. St. And., F.F.R.

OF THE M.R.C. GROUP FOR RESEARCH INTO THE GENERAL EFFECTS OF RADIATION, WESTERN GENERAL HOSPITAL, EDINBURGH, 4

HUGH FORREST
M.B. Glasg.

SURGICAL REGISTRAR, ROYAL HOSPITAL FOR SICK CHILDREN AND WESTERN INFIRMARY, GLASGOW

J. R. ROY
M.B. Glasg., F.R.F.P.S., M.R.C.P.E., D.P.M.

SENIOR REGISTRAR IN PSYCHOLOGICAL MEDICINE, SOUTHERN GENERAL HOSPITAL, GLASGOW

JOHN S. S. STEWART *
M.B. Glasg.

LATE SURGICAL REGISTRAR, ROYAL INFIRMARY, GLASGOW

BERNARD LENNOX
M.D. Durh., Ph.D. Lond., F.R.F.P.S., M.R.C.P.

SENIOR LECTURER, DEPARTMENT OF PATHOLOGY, UNIVERSITY AND WESTERN INFIRMARY, GLASGOW

AMONG the various groups of human sexual anomalies there are three in which the nuclear sex is at variance with the phenotypic sex. These are (1) the chromatin-positive cases of Klinefelter's syndrome, (2) the chromatin-negative cases of Turner's syndrome and gonadal dysgenesis in apparent females, and (3) apparent females who are chromatin-negative on nuclear sexing and who have the features of the testicular feminisation syndrome. It has recently been shown that the first anomaly is due to the presence of an extra sex chromosome, so that these patients are XXY (Jacobs and Strong 1959, Ford, Jones, Miller, Mittwoch, Penrose, Ridler, and Shapiro 1959; Ford, Polani, Briggs, and Bishop 1959), and that the second anomaly depends on the absence of one sex chromosome, so that these patients are XO (Ford, Jones, Polani, Almeida, and Briggs 1959). We report here the determination of chromosomal sex in four instances of the third anomaly—testicular feminisation.

In the complete expression of this syndrome the external genitalia are female, pubic and axillary hair are absent or scanty, the habitus at puberty is typically female, and there is primary amenorrhoea. Testes can be found either within the abdomen, or in the inguinal canals, or in the labia majora, and as a rule the vagina is incompletely developed. An epididymis and vas deferens are commonly present on both sides, and there may be a rudimentary uterus and fallopian tubes. The condition is familial and is transmitted through the maternal line (Grumbach and Barr 1958).

* Present address: Department of Surgery, Queen's College, Dundee.

Cases and Investigation

Case 1, born in 1949, was admitted to hospital in February, 1958, for repair of inguinal herniæ. The vagina was about 2 cm. long, terminated in a blind pouch. During the repair of the herniæ a recognisable testis was found in each inguinal canal. At laparotomy last May the testes were seen to be in the position normally occupied by the ovaries, and there were neither uterus nor fallopian tubes. Histologically the left gonad showed the features of a prepubertal undescended testis. The patient's mental development was normal for her age. The nuclear sex, as determined from skin biopsy material and buccal smears, was chromatin-negative. Colour-vision was normal.

Case 2, born in 1957, was admitted in May, 1958, for the repair of inguinal herniæ. The right inguinal canal contained a small testis, with the same histological features as in case 1. A vagina 1–2 cm. long was present, but there was no evidence of a cervix and no uterus was palpable. In view of the child's age tests of intelligence and of colour-vision were not undertaken. The nuclear sex (skin biopsy and buccal smears) was chromatin-negative.

Case 3, born in 1926, has been admitted to hospital three times for mental depression. She has primary amenorrhoea, and in 1947 she was told that she had no uterus. On examination in 1958 little pudendal hair was present and no pubic or axillary hair. Breast development was normal, but the vagina was only about 5 cm. in length and there was no evidence of a uterus. The patient was of less than average intelligence, and was found to be colour-blind. The nuclear sex of a skin biopsy was chromatin-negative.

Case 4, born in 1936, was admitted in March, 1951, because of bilateral inguinal swellings and primary amenorrhoea. Breast development was normal, but pubic and axillary hair were absent. At laparotomy neither uterus nor fallopian tubes were found. Histological examination of material from the gonads showed testicular tissue. The nuclear sex (skin biopsy and buccal smears) was chromatin-negative. The patient had normal colour-vision, but a similarly affected sister and a normal brother were colour-blind.

Chromosome Examination

Sternal marrow from cases 1, 2, and 4, and iliac-crest marrow from case 3, were cultured and treated as described by Ford, Jacobs, and Lajtha (1958). The chromosome-counts are shown in the table.

In all four marrows the great majority of cells had a normal diploid content of 46 chromosomes. There is no evidence that, in these four marrows, departures from this number are due to any cause other than artefacts produced during the preparation of the material.

Only one cell in case 1 was suitable for detailed analysis, but several suitable cells were available from cases 2 and 3, and many from case 4. In all the cells analysed in detail there were 5 small acrocentric chromosomes and 15 medium-sized metacentric chromosomes, indicating that the normal

CHROMOSOME-COUNTS ON MARROW CELLS: DISTRIBUTION OF CHROMOSOME NUMBERS IN EACH CASE

Chromosome number		42	43	44	45	46	47	48	4n	8n	8n<
No. of cells counted	Case 1	1	0	2	3	32	2	2	0	1	1
	Case 2	1	0	0	2	11	0	0	0	0	0
	Case 3	1	0	1	2	28	1	0	0	0	0
	Case 4	0	0	0	2	21	0	0	0	0	0

male complement of one X chromosome and one Y chromosome was present (see figure).

Discussion

The observation that these patients with the testicular feminisation syndrome have a normal diploid number of chromosomes and an XY chromosomal sex is consistent with the observation that they are chromatin-negative, and excludes an aberration of chromosome number as the cause of the disorder. The latter explanation, which would imply an XXY constitution in these cases, has been discussed by several authors (Petterson and Bonnier 1937, Beatty 1957, Danon and Sachs 1957). Nucleolar chromocentre anomalies were described by Danon and Sachs who regarded these as evidence of the presence of three sex chromosomes; but such an interpretation of nucleolar chromocentre appearances is probably not reliable (Lennox, Serr, and Ferguson-Smith 1959). Of the skin biopsies taken in these cases, though all were sufficient for recognition of sex chromatin, only two were of the very high quality needed for studies of nucleolar

Chromosomes of bone-marrow cell of case 4, arranged in pairs and showing the presumptive X and Y.

chromocentres. Neither of these showed any unusual frequency of nuclei with three such chromocentres. Furthermore, the colour blind state of case 3 and of the sister of case 4 makes it very improbable that two X chromosomes are present (Stewart 1959).

Our findings support the suggestion of Grumbach and Barr (1958) that testicular feminisation is associated with either a sex-linked recessive gene or a sex-limited autosomal dominant gene. Apparent females with testicular feminisation are sex-reversed males. This is consistent with the results of analysis of the familial cases, which shows that the ratio of females to the sum of the affected males and normal males does not significantly differ from an expected ratio of 1 to 1 (Grumbach and Barr 1958).

Our thanks are due to Mr. W. M. Dennison, Prof. T. Ferguson Rodger, and to Dr. E. G. Oastler for permitting us to examine their cases. We are also grateful to Miss M. Brunton for technical assistance.

REFERENCES

Beatty, R. A. (1957) Parthenogenesis and Polyploidy in Mammalian Development; p. 54. London.
Danon, M., Sachs, L. (1957) *Lancet*, ii, 20.
Ford, C. E., Jacobs, P. A., Lajtha, L. G. (1958) *Nature, Lond.* **181,** 1565.
— Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. (1959) *Lancet*, i, 709.
— — Polani, P. E., Almeida, J. C. de, Briggs, J. H. (1959) *ibid.* p. 711.
— Polani, P. E., Briggs, J. H., Bishop, P. M. F. (1959) *Nature, Lond.* **183,** 1030.
Grumbach, M. M., Barr, M. L. (1958) *Recent Prog. Hormone Res.* **14,** 255.
Jacobs, P. A., Strong, J. A. (1959), *Nature, Lond.* **183,** 302.
Lennox, B., Serr, D. M., Ferguson-Smith, M. A. (1959) *J. Endocrin.* (in the press).
Petterson, G., Bonnier, G. (1937) *Hereditas*, **23,** 49.
Stewart, J. S. S. (1959) *Lancet*, ii, 592.

TESTICULAR FEMINISATION AND COLOUR-BLINDNESS

JOHN S. S. STEWART *
M.B. Glasg.
LATE SURGICAL REGISTRAR, GLASGOW ROYAL INFIRMARY

TESTICULAR feminisation or hereditary male pseudo-hermaphroditism is a well-recognised type of intersexuality (Petterson and Bonnier 1937, Morris 1953). The ætiology and genetic mechanism is still disputed. Witschi et al. (1957) suggested that a maternal factor causes feminisation of every male fœtus. Danon and Sachs (1957) and Beatty (1957) suggested that an abnormal XXY chromosomal complex might be the cause. Although recording no pedigrees, Lenz (1957) knew of two colour-blind patients with testicular feminisation, and discussed the value of colour-blindness studies in this syndrome. Two pedigrees of testicular feminisation and colour-blindness are described here. The chromosomal sex of two of the affected subjects has been determined (Jacobs et al. 1959).

Case-reports and Genetic Investigations

Two families in which testicular feminisation and colour-blindness occur have been investigated. The pedigree of family A is shown in fig. 1 and of family B in fig. 2. The features of the syndrome are illustrated by case 1. Habitus is female with good breast development but pubic and axillary hair is absent (fig. 3). The gonads were partially descended in inguinal herniæ, and biopsy confirmed that they were sterile testes (fig. 4). This patient has a normal brother. In both families all available subjects were tested for colour-blindness with the 8th Japanese edition of Ishihara's plates (see table) and some were examined with the Nagel anomaloscope.

Family A (fig. 1)

(I. 1).—No information available.

(I. 2).—Aged 50. Normal colour-vision. (This subject made 13 mistakes, but not of the type made by a colour-blind person. They were due, at least in part, to rather low intelligence.) Anomaloscope test normal. The fifth of six children. Two brothers reputed to have normal colour-vision. Three sisters

* Present address: Department of Surgery, Queen's College, Dundee.

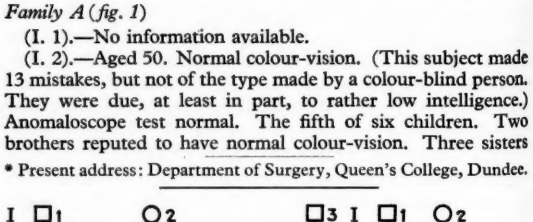


Fig. 1—Pedigree of Family A.

Fig. 2—Pedigree of Family B. Symbols as in fig. 1.

reputed to have normal colour-vision and normal menstrual history.

(I. 3).—Reputed colour-blind. Died two years ago, aged 51, from "lung trouble". No brothers or sisters.

(II. 1).—Aged 32. Illegitimate. Reputed normal colour-vision. Married with several children.

(II. 2).—Aged 28. Reputed normal colour-vision and normal menstruation.

(II. 3).—*Case* 1. Aged 23. This patient, index case of the sibship, presented at age of 15 with primary amenorrhœa and inguinal swellings. Breasts were well developed and pubic and axillary hair absent. Vagina ended blindly, and absence of uterus and tubes was confirmed by laparotomy. Bilateral biopsy confirmed that the gonads were sterile testes (fig. 4). The gonads were later removed. At the age of 23 the patient presents the typical features of the syndrome (fig. 3). Colour-vision is normal by Ishihara and anomaloscope. Chromosomal sex is that of a normal male (Jacobs et al. 1959, case 4).

Fig. 3—Case 1. Note well-developed breasts and absent pubic hair.

(II. 4).—Aged 17. Male who shaves daily. Completely normal in appearance and on clinical examination, with pubic, axillary, and abdominal hair of male distribution. Normal-sized testes are descended in a rugose scrotum. Phallus normal in size and appearance with a fully developed penile urethra. Colour-blind: 24 mistakes by Ishihara test. Anomaloscope test: extreme deuteranomaly with vision nearly dichromatic.

(II. 5).—*Case 2.* Aged 13. Probable case of testicular feminisation. Has not yet menstruated. Slight breast development. Pubic and axillary hair absent. Nuclear sex chromatin-negative. Colour-blind: 22 mistakes by Ishihara test. Anomaloscope test: extreme deuteranomaly, similar in type to that of her brother (II. 4) but slightly less extreme. The difference in testing between these subjects (II. 4 and II. 5) could be attributed to their personalities. A variation of similar degree is found in sibs affected by the same type of colour-blindness.

Family B (fig. 2)

The patient (II. 2) and her elder brother (II. 1) are refugees from Central Europe and investigation of the family was not possible. Both parents (I. 1) and (I. 2) are presumed dead, and no accurate information is available about colour-vision or menstrual history of relatives. Both parents are reputed to have had normal colour-vision.

(II. 1).—Apparently normal male, not examined clinically. Colour-vision normal by Ishihara test.

(II. 2).—*Case 3.* Aged 32. Presented at a psychiatric unit with depression. Has never menstruated. Vagina short with absent uterus; pubic and axillary hair absent. Nuclear sex chromatin-negative. Colour-blind: 24 mistakes by Ishihara test. Anomaloscope test: extreme deuteranomaly. Chromosomal sex is that of a normal male (Jacobs et al. 1959, case 3).

Discussion

The hypothesis of Witschi et al. (1957) that a maternal anti-testis factor causes feminisation of male fœtuses would be an attractive one, but for the fact that not every male is affected. Witschi et al. recognised that some normal males have been described in the same sibship as affected pseudo-hermaphrodite males, but noted that only one such male is reported as having fathered children, and suggested that probably none of the males had been carefully examined. In the present pedigrees one of the males has had a full clinical examination and is normal. In particular, testes are fully descended and the phallus is normal in size with a fully developed penile urethra. There is, therefore, no evidence to suggest that the fœtal testis had not exerted its usual morphogenetic action. Clinical examination thus provides strong evidence against Witschi's hypothesis, and the report (Morris 1953) of a case of testicular feminisation with a twin brother seems to exclude it completely. Witschi's hypotheses was in part based on the paucity of males in reported sibships; but in the series of Petterson and Bonnier (1937) the paucity of males is not significant—the apparent significance was due to a statistical error (Bonnier 1938).

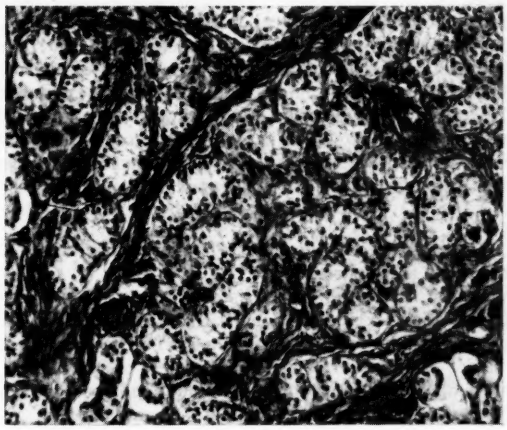


Fig. 4—Small seminiferous tubules with absent germ cells. (Masson ×135.)

Bonnier (1938) pointed out that the condition may be caused by a sex-linked recessive or a sex-controlled (sex-limited) autosomal dominant factor. These possibilities are difficult to distinguish since affected subjects are sterile, but some information can be obtained from a study of pedigrees in which sex-linked recessive characters are also present. An autosomal factor segregates independently of the sex chromosomes, and two sex-linked characters may be separated by crossing over. If the latter are not closely linked, crossing over can give the appearance of random segregation. Thus colour-blindness studies, even in a large number of families, may provide only limited evidence about the genetics of testicular feminisation. Although two colour-blind cases

READINGS OF SUBJECTS TESTED WITH ISHIHARA'S PLATES (8TH JAPANESE ED.)

Subject	No. of mistakes	Reading of plate no.																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
A I. 2	13	12	8	6	20	28	..	8	15	24	..	6	..	4	5	2	..	..	5	8	..	..	26	42	35	96
A II. 3	6	12	8	6	20	57	5	3	15	74	8	6	97	40	5	7	76	..	..	..	..	..	26	43	35	96
A II. 4	24	12	3	5	70	85	2	5	17	21	..	..	..	..	..	..	..	..	5	2	45	78	2	..	8	..
A II. 5	22	12	8	6	20	35	2	5	17	21	..	..	..	..	..	..	..	..	5	2	45	23	2	8	8	9
B II. 1	3	12	8	6	29	57	5	8	15	71	2	6	97	45	5	7	16	78	..	..	..	..	26	42	35	96
B II. 2	24	12	3	5	70	35	2	5	17	21	..	..	..	..	..	..	..	..	5	2	45	73	2	4	3	9
Correct reading	..	12	8	6	29	57	5	3	15	74	2	6	97	45	5	7	16	73	..	..	..	..	26	42	35	96

of testicular feminisation are known (Lenz 1957) the present pedigrees are believed to be the first in which testicular feminisation and colour-blindness are recorded.

The presence of an abnormal XXY sex-chromosomal constitution is excluded by studies of bone-marrow cells in mitosis (Jacobs et al. 1959). The cytogenic evidence is that subjects with testicular feminisation have only one X chromosome. The incidence of colour-blindness in the condition—two colour-blind in the first three patients tested in Glasgow—is genetic evidence in support of this. Since the cases of testicular feminisation have an X and a Y chromosome, the X is clearly inherited from the mother; and it is unimportant, for the present study, that the father of neither family was available for testing. Case 2 is too young for a firm clinical diagnosis to be made but the chromatin-negative nuclear sex is acceptable confirmation of the diagnosis. Since this subject with testicular feminisation is colour-blind, but her similarly affected sister (case 1) is colour-normal, this suggests that the genetic factors responsible for testicular feminisation and colour-blindness are not closely linked on the X chromosome. It does not, however, exclude the possibility of crossing over, between linked loci. In the second pedigree (family B) the mother must be heterozygous for colour-blindness since she has a colour-normal son (II. 1) and a colour-blind daughter (II. 2) who is case 3. The family provides some information of value in the assessment of linkage with the X chromosome. Clearly, however, a study of many pedigrees with colour-blindness and testicular feminisation is necessary.

Summary

Two pedigrees of testicular feminisation and colour-blindness are reported.

In the first sibship two sisters suffer from testicular feminisation. One is colour-normal, the other colour-blind. A colour-blind brother is a normally developed male.

In the second sibship a colour-blind patient with testicular feminisation has a colour-normal brother.

It is a pleasure to acknowledge my indebtedness to Dr. E. G. Oastler and Prof. T. Ferguson Rodger for permission to publish cases. I am grateful also to Prof. R. W. Pickford for anomaloscope testing and to Prof. T. Symington for access to biopsy specimens.

REFERENCES

Beatty, R. A. (1957) Parthenogenesis and Polyploidy in Mammalian Development; p. 54. London.
Bonnier, G. (1938) *Hereditas, Lund*, **24**, 465.
Danon, M., Sachs, L. (1957) *Lancet*, ii, 20.
Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Forrest, H., Roy, J. R., Stewart, J. S. S., Lennox, B. (1959) *ibid.* ii, 591.
Lenz, W. (1957) *Acta genet. med. gemell.* **6**, 231.
Morris, J. McL. (1953) *Amer. J. Obstet. Gynec.* **65**, 1192.
Petterson, G., Bonnier, G. (1937) *Hereditas, Lund*, **23**, 49.
Witschi, E., Nelson, W. O., Segal, S. J. (1957) *J. clin. Endocrin.* **17**, 737.

"... This isolation of the individual will probably grow, for the universal tendency now is to increase specialisation at the expense of general education. This is a tragedy, not only for each person concerned, but also for society. Nothing is easier than to manipulate men who are specialists, and have no knowledge or understanding outside their own fields. It is paradoxical, but true, that the age of common education may well weaken democracy. To avert the danger of intellectual aristocrats ruling helot specialists, the universities should aim at providing all students with sufficient historical, cultural and scientific knowledge to understand the world in which they live and the role which they, as specialists, are to play in society."—JASPER UNGOED-THOMAS, *New Statesman*, Oct. 10, 1959, p. 464.

CHOLESTERYL ESTER FATTY ACIDS IN ATHEROMA AND PLASMA

A. S. WRIGHT
B.Sc. Lpool
RESEARCH FELLOW

G. A. J. PITT
B.Sc., Ph.D. Lpool
LECTURER

R. A. MORTON
D.Sc. Lpool, F.R.S.
JOHNSTON PROFESSOR

DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LIVERPOOL

ONE of the most clear-cut hypotheses regarding atherogenesis is that of Sinclair (1956, 1957, 1958a and b). Briefly, it assumes that essential fatty acids are required for the normal transport and metabolism of cholesterol. When there is a relative deficiency of essential fatty acids, cholesterol becomes esterified instead with saturated acids or with "unnatural" isomers of essential fatty acids. Such esters, according to the hypothesis, accumulate or are deposited in tissues—causing, among other things, atheroma. Recent work by Ahrens et al. (1959) indicates that the hypothesis might have to be extended to include as beneficial certain polyunsaturated acids other than those normally accepted as "essential". The key assertion of Sinclair's hypothesis remains, however, that the fatty acids esterified with cholesterol in atheromatous tissue either will be more saturated or will contain more of the unnatural isomers than those esterified with cholesterol in normal plasma.

Our own investigations, described below, were aimed at ascertaining how much difference in saturation there might be between cholesteryl esters in normal blood and in atheromatous tissues.

Methods

The tissues used were obtained at postmortem examinations carried out by the department of pathology of this university. They were sent to us without delay and the total lipid was then extracted as quickly as possible.

Extraction Procedures

Plaques.—After being cut out, they were extracted with ethanol at room temperature, and then ground to a fine powder in a mortar with successive portions of ether until all the soluble lipid had been removed.

Wall tissue.—The adventitia was stripped off and the remaining tissue chopped into small pieces and extracted in the same way as the plaques.

Plasma.—A mixture of methylal and methanol (4/1 v/v) (Delsal 1944) was used as the extractant. The precipitate which formed was re-extracted with the same solvent, then with ether.

Chromatography.—Cholesteryl esters and free cholesterol were separated from other lipid components by chromatography on acid-washed alumina (Peter Spence, grade O). For the present work we found it much better than silicic acid. Sterol esters could be recovered quantitatively without hydrolysis. No isomerisation or oxidation took place which could be detected by ultraviolet spectrophotometry or iodine value determinations.

Iodine values.—A semi-micro method was adapted from that of Rosenmund and Kuhnhenn (1923) which could be used either on the fatty acids freed by acidifying the saponification liquor or on the unhydrolysed cholesteryl esters. The free acids gave iodine values about 2% lower than when in the intact ester.

We hope to describe these procedures in more detail elsewhere.

Fatty-acid analysis.—Polyunsaturated fatty acids were determined by the alkali-isomerisation method following

Holman and Hayes (1957). The di-, tri- and tetra-enoic acids are recorded as linoleic, linolenic, and arachidonic acids, which is probably largely true, even though the method counts as one all the acids with the same methylene-interrupted series of double bonds. Trans-isomers interfere only slightly. The monoenoic-acid content was determined by the difference between the iodine value and the sum of the contributions due to polyunsaturated acids.

Cholesterol.—Kenny's (1952) method was used.

Statistical methods.—The procedures described by Snedecor (1946) were employed.

Results

When our experimental work was almost complete, three reports were published in which the fatty acids esterified with cholesterol (C.F.A.) in plasma and atheromatous tissues were compared (Lewis 1958, Luddy, Barford, Riemenschneider, and Evans 1958, Tuna, Reckers, and Frantz 1958). The results are shown, together with ours, in tables I and II.

TABLE I—FATTY ACIDS ESTERIFIED WITH CHOLESTEROL IN ATHEROMATOUS TISSUE

Group	Present authors ‡	Luddy et al. (1958)	Lewis (1958)	Tuna et al. (1958)*
Iodine value ..	115 (±7) (27)	134	64	Approx. 140
% Linoleic ..	29·5 (±2·8) (15)	23·6	11·0	37·6
% Linolenic ..	3·0 (±0·8) (15)	1·4	3·3	1·6
% Arachidonic	4·7 (±1·2) (15)	7·0	3·6	7·4
% Pentaenoic ..	1·0 (±0·4) (15)	1·3	0·3	0·9
% Hexaenoic ..	0·5 (±0·2) (15)	1·0	0·4	1·0
% Monoenoic ..	35·1 (±5·2) (15)	61·5	22·1†	41·3
% Saturated ..	26·1 (±2·9) (15)	4·2	59·3†	10·7

* Polyunsaturated acid figures taken from alkali isomerisation results; monoenoic and saturated acid figures from gas chromatography results. They do not add up to exactly 100%; the iodine value (calculated by us) is therefore approximate.
† Calculated from author's data.
‡ Expressed as mean (±standard deviation) (number of specimens).

We found the C.F.A. in plasma to have an unmistakably higher iodine value and linoleic-acid content, and a much lower saturated-acid content, than the C.F.A. from aortas. The plasma-C.F.A. contained significantly more linolenic ($P < 0.01$) and probably significantly more arachidonic acid ($P < 0.02$). Differences were not significant in monoenoic ($0.3 < P$), pentaenoic ($0.5 < P$) and hexaenoic acid ($0.1 < P$) contents.

Comparison of our results with those of other workers (tables I and II) reveals substantial differences between the four sets of findings. It is possible that the data in table I are not all strictly comparable. Our figures and those of Luddy et al. refer to the C.F.A. from the plaques and walls of atheromatous aortas; those of Tuna et al. to the plaques only; and those of Lewis to atheromatous coronary arteries.

We have examined separately the cholesteryl esters from plaques alone and compared them with those left in the wall after cutting out all plaques. There were no significant differences (see table III). In four cases, atheromatous ulcers, calcified plaques, and "soft" plaques were separated from each other; only slight differences in unsaturation were found in the C.F.A. The divergences between our results and those of Luddy et al. and of Tuna et al. are therefore unlikely to be due to the use of plaque material only by the last group.

TABLE III—FATTY ACIDS ESTERIFIED WITH CHOLESTEROL IN PLAQUES AND WALLS OF AORTAS (MEAN AND STANDARD DEVIATION)

—	No. of aortas	Plaques	Walls
Iodine value	23	116 (±5)	117 (±5)
% Linoleic	12	30·0 (±2·8)	30·7 (±3·0)
% Linolenic ..	12	2·9 (±0·7)	3·0 (±0·7)
% Arachidonic ..	12	5·0 (±0·9)	4·6 (±0·8)
% Pentaenoic ..	12	1·1 (±0·4)	1·0 (±0·3)
% Hexaenoic ..	12	0·6 (±0·2)	0·6 (±0·2)
% Oleic	12	34·3 (±5·7)	35·2 (±4·3)
% Saturated ..	12	26·2 (±3·5)	25·1 (±3·1)

The lipids from atheromatous coronary arteries do not have the same composition as those from aortas (Böttcher et al. 1959). Different fatty acids could be esterified with cholesterol in the two sites, which might be why Lewis's results bear little resemblance to the others.

We investigated the C.F.A. in various tissues obtained from a 53-year-old male who had suffered from coronary disease for one year before a fatal coronary thrombosis; the coronary arteries were laden with gross lipid deposits. Three more cases of death from coronary thrombosis were investigated similarly, but the coronary artery material was bulked because there was not enough to examine all three separately. The fatty acids esterified with cholesterol in different tissues are compared in table IV. Too much should not be claimed on the basis of such limited data, but the results make it unlikely that the composition of the cholesteryl esters in coronary arteries will in general differ substantially from those in aortas—certainly not to the extent of the discrepancy between the results of Lewis and those of the other investigators shown in table I.

TABLE IV—FATTY ACIDS ESTERIFIED WITH CHOLESTEROL IN AORTA, CORONARY ARTERIES, AND LIVER

—	53-year-old man			3 other cases		
	Aortas	Plaques * from coronary arteries	Liver	Aortas (mean)	Coronary arteries (bulked)	Liver (mean)
Iodine value ..	116	116	110	115	110	106
% Linoleic ..	28·0	27·0	24·2	27·9	24·9	24·6
% Linolenic ..	4·5	3·7	4·1	2·8	3·2	2·7
% Arachidonic	5·0	4·0	6·0	4·8	4·2	4·1
% Pentaenoic	1·2	0·8	1·0	0·9	0·7	0·8
% Hexaenoic ..	0·5	0·4	0·6	0·5	0·4	0·5
% Oleic ..	32·3	42·8	31·3	38·1	41·4	38·2
% Saturated ..	28·5	21·3	32·8	24·9	25·2	29·1

* Cholesteryl-ester fatty acids in the wall after removal of plaques had an iodine value of 114. Not enough was available for fatty-acid analysis.

Although the figures of table I are for cholesteryl esters from different sites, it seems reasonable to expect that they should be approximately the same. In fact the results of the four groups of workers are grossly different.

TABLE II—FATTY ACIDS ESTERIFIED WITH CHOLESTEROL IN PLASMA (EXPRESSED AS MEAN, STANDARD DEVIATION, AND NUMBER OF SUBJECTS)

Group	Present authors	Luddy et al. (1958)	Lewis (1958)		Tuna et al. (1958)*
			Normals	Coronary-artery disease	
Iodine value	146 (±7) (31)	143	160 (±34·5) (8)	136 (±35·6) (12)	Approx. 131
% Linoleic	43·8 (±3·5) (12)	47·5	53·2 (±10·7) (8)	40·6 (±15·5) (12)	41·1
% Linolenic	4·0 (±0·8) (12)	0·7	5·1 (± 2·5) (8)	5·4 (± 2·8) (12)	0·7
% Arachidonic	6·1 (±1·5) (12)	8·0	9·5 (± 2·3) (8)	7·6 (± 3·0) (12)	6·2
% Pentaenoic	0·8 (±0·3) (12)	0·9	1·4 (± 0·5) (8)	2·1 (± 1·0) (12)	0·7
% Hexaenoic	0·7 (±0·4) (12)	0·7	2·5 (± 2·7) (8)	2·8 (± 2·7) (12)	1·2
% Monoenoic	32·7 (±6·9) (12)	23·5	0·9†	1·0†	28·6
% Saturated	11·9 (±3·9) (12)	18·7	27·4†	40·5†	16·2

* See footnote to table I.
† Means, calculated from author's data.

Technical difficulties in this field are not negligible; the presence of higher polyunsaturated acids can cause determinations of iodine value to err on the low side, and can lead to unreliable results with the alkali isomerisation method. With the latter, sizeable differences between laboratories do occur, but they could scarcely account for the wide discrepancies in table I. Within a particular laboratory, more reproducible results are obtained; the comparison between the cholesteryl esters in plasma and atheromatous tissue determined in the same laboratory (compare tables I and II) should still test the validity of the Sinclair hypothesis. In fact the results give no clear answer.

Lewis's figures in general agree with Sinclair's hypothesis; Luddy et al. found less of the essential fatty acids in atheromatous tissue than in blood, but nevertheless they did find substantial amounts. Our results are similar to those of Luddy et al., but the differences between blood and aorta are less. Tuna et al. found only small differences in essential fatty acid content.

The general picture is confused. Discrepancies between groups of investigators are large in the figures for atheromatous tissues and real though smaller for the plasma esters.

Cholesteryl Esters of Plasma

The results of Luddy et al. and of Tuna et al. do not fall outside our range, with the exception of linolenic acid for which technical errors are proportionately large. Lewis's normal subjects had significantly higher amounts of linoleic ($P \simeq 0{\cdot}01$) and arachidonic acids ($P \simeq 0{\cdot}001$) than our normals. The latter resembled more Lewis's coronary patients; a comparison showed no significant differences in total unsaturation or individual polyunsaturated fatty acids.

Our blood samples were obtained from a mixed set of subjects, mainly male and under 30 years of age, on a normal diet. The esterified and total plasma-cholesterol values were determined separately on nineteen of them; the means ($\pm$ standard deviation) were 146 (± 17) and 249 (± 39) mg. per 100 ml. respectively. (These figures were higher than expected; it is hoped to investigate why this is so.) No attempt was made to collect samples in the post-absorptive state, the object being to gain some information of the normal range of plasma C.F.A. In the circumstances, perhaps the most remarkable feature of our results in table II is their relatively narrow range.

We found a correlation between the C.F.A. iodine value and the content of linoleic acid ($P < 0{\cdot}01$) and arachidonic acid ($P < 0{\cdot}02$). There was an inverse correlation between iodine value and oleic acid content, but it was not significant ($0{\cdot}05 < P < 0{\cdot}1$); there was no inverse correlation between iodine value and saturated acids. In short, it appears that the iodine value of the plasma esters is chiefly influenced by the linoleic and arachidonic acid content (cf. Lewis 1958).

If these findings can be confirmed by other workers and shown to be general, much useful information could perhaps be obtained by the relatively simple procedure of separating plasma cholesteryl esters on an alumina column and determining the iodine value without saponification. This can all be done on less than 5 ml. blood.

Lewis (1958) reported that in his series of subjects he found an inverse correlation ($P < 0{\cdot}05$) between the C.F.A. iodine value and the plasma ester-cholesterol level. We confirmed this, obtaining a more significant correlation ($P < 0{\cdot}02$). We also found an inverse relationship, although less marked ($P < 0{\cdot}05$), between the C.F.A. iodine value and total plasma cholesterol level. This can be ascribed mainly to the ester fraction, since the inverse relationship between C.F.A. iodine value and plasma free cholesterol was much poorer ($0{\cdot}1 < P < 0{\cdot}2$).

Several workers have recently demonstrated that large doses of unsaturated fatty acids will lower the total blood-cholesterol level and raise the C.F.A. iodine value, but the amounts given are usually in excess of those to be expected in any reasonable diet. It is interesting that a similar inverse relationship appears to hold in our normal subjects, and for at least the cholesterol-ester level in Lewis's subjects.

So far as we can trace, no other workers have attempted such a correlation, and figures for the iodine values of plasma-C.F.A. are scarce. The oft-quoted data of Bloor et al. (1938) cannot be used because they are based on an unreliable method (Kelsey 1939). We therefore examined the results of Kinsell et al. (1958) to see if they show an inverse relationship between the iodine values of C.F.A. and the total blood-cholesterol level. There was no correlation in his case of hypercholesterolæmia; it was poor in the cases of mild diabetes ($0{\cdot}05 < P < 0{\cdot}1$) and of xanthomatosis associated with diabetes ($0{\cdot}1 < P < 0{\cdot}2$) but very significant ($P < 0{\cdot}001$) in the 19-year-old youth with a fractured femur. It would be of interest to know if this inverse relationship holds generally except in certain metabolic disorders.

Cholesteryl Esters of Atheromatous Tissue

The largest discrepancies between the four groups of workers lie in the figures for atheromatous tissue (table I). Ours have been determined on individual cases and fall within a fairly narrow range. The figures of Luddy et al. and of Tuna et al. refer to bulked material from several cases; those of Lewis are the mean of four. Yet most of these figures fall outside the range of our extreme values. It is easier to detail those figures which do fall within our range. They are: Luddy et al., only pentaenoic acids; Tuna et al. only hexaenoic and monoenoic; Lewis, linolenic, arachidonic, penta- and hexa-enoic acid contents. None of our determinations of the important quantities, iodine value, linoleic acid, and saturated-acid content, reaches the figures obtained by the other workers. Böttcher et al. (1958) have also published a range of results for some fatty acids; that for saturated acids covers ours; for linoleic acid, it overlaps with ours, but is rather lower; there is also an overlap with monoenoic acids but theirs is clearly higher.

These five reports of C.F.A. in atheroma differ beyond what could readily be attributed to technical shortcomings. Is there some variable as yet unrecognised? We have made a preliminary attempt to find it, using our limited data.

In this, we worked only with the iodine values of the C.F.A., because we have too few results on the fatty-acid composition. The use of iodine values, although not wholly satisfactory, seems legitimate in a preliminary investigation of C.F.A. of aortas, since in eighteen samples analysed for fatty acids there was a correlation between the iodine value and the linoleic-acid content ($P < 0{\cdot}05$) and arachidonic-acid content ($P < 0{\cdot}001$). The saturated-acid content tended to vary inversely with the iodine value ($P < 0{\cdot}05$), as did the monoenoic content, but not significantly ($0{\cdot}05 < P < 0{\cdot}1$). In short, the iodine value tends to reflect the content of essential fatty acids and has a (less marked) inverse relationship to the saturated and perhaps monoenoic acids.

We compared the iodine value of the C.F.A. from atherosclerotic aortas of patients who died from coronary thrombosis (group I), of those who had atherosclerosis but died from other causes (group II), and from aortas showing no streaks or visible signs of fatty infiltration (group III). We call group III

"normal", although it is doubtful what should be considered normal in this context. All the tissues in group III were from persons under 29 years of age, with a mean lipid content less than 1% of the total wet weight of tissue. The C.F.A. iodine value in group I (mean, 119; standard deviation, ±5; number of cases, 10) was higher ($P < 0.02$) than group II (112±7 [14]) and group III (109±9 [8]) ($P < 0.01$). There was no significant difference in iodine value between groups II and III.

No claim is made that a higher iodine value is correlated with a tendency to coronary infarction, for groups I and II were not comparable in all respects. They had roughly the same age distribution, but there were sex differences; group I contained only males, group II (and III) both sexes. Atheromatous males had higher figures (117±5 [19]) than atheromatous females (111±10 [8]) of comparable ages ($P < 0.05$); but, as the male group contained far more cases of coronary thrombosis, this comparison in turn may not be valid. Our data are not extensive enough to separate statistically the differences due to sex or cause of death.

The C.F.A. iodine value tended to rise with increasing atherosclerosis (as measured by the percentage lipid in the original material), which appears to be in agreement with the results of Böttcher et al. (1958), but the correlation in our series was not significant ($P < 0.1$).

Whatever the explanation of these findings, it appears that neither the extent of atherosclerosis nor the presence of coronary infarction is associated with a relative deficiency of essential fatty acids in these esters. In the C.F.A. of young healthy aortas, the essential-fatty-acid content tends to be lower than that of heavily atherosclerosed tissue.

It is difficult to get the necessary information on healthy aortas, because they contain very little esterified cholesterol, and the chance of experimental error is greatly increased. For example, one aorta from a youth of 19 contained only 2 mg. of cholesteryl esters (compared with about 1 gm. in many atherosclerotic aortas of similar size). The C.F.A. were found to have an iodine value of 64. With such small amounts of material great accuracy is unlikely. This case was therefore not included in group III above, but at the worst the result would not be expected to depart from the truth by as much as a third. The C.F.A. in this very healthy aorta are therefore very much more saturated than in an atherosclerotic specimen.

The new results in this paper agree with the accepted view that plasma-cholesterol is preferentially esterified with essential fatty acids. The "non-transport" forms of cholesteryl esters are rather more saturated, but those in atheromatous tissues appear to be no more saturated, and perhaps are rather less saturated, than those found in liver where esterified cholesterol occurs naturally.

When the variation in results obtained for the C.F.A. of atheromatous tissue is considered, it is at this stage clearly premature to use any one set of results to support any hypothesis of atherogenesis. Why the various groups of workers differ so much is thus a pressing problem.

Summary

The fatty acids esterified with cholesterol (C.F.A.) have been compared in atheromatous tissues and in plasma. Three other groups of workers have also done this; there are striking differences between the four sets of results.

The iodine value of the C.F.A. of plasma and aortas is correlated with their essential fatty acid content.

There is an inverse relationship between the iodine value of plasma C.F.A and the plasma cholesterol-ester level.

The C.F.A. of plaques in aortas are similar to those of the walls of atheromatous aortas and do not show large differences from those in coronary arteries.

The essential fatty acid content of C.F.A. of atheromatous tissue was no lower in cases of death from coronary thrombosis than in cases of death from other causes; in neither was it less than in normal healthy aortas.

At present the evidence is too discrepant to lend support to a theory of atherogenesis based specifically on differences in C.F.A. in plasma and atheroma.

We thank Prof. H. L. Sheehan and Dr. A. H. Cruickshank of the department of pathology of the University of Liverpool for supplying tissues and for helpful advice; and Dr. T. Black, of Liverpool Royal Infirmary, and Dr. D. Lehane, medical director of the Liverpool Regional Blood Transfusion Service, for providing blood samples.

REFERENCES

Ahrens, E. H., Insull, W., Hirsh, J., Stoffel, W., Peterson, M. L., Farquhar, J. W., Miller, T., Thomasson, H. J. (1959) *Lancet*, i, 115.
Bloor, W. R., Blake, A. G., Bullen, S. S. (1938) *J. Allergy*, **9**, 227.
Böttcher, C. J. F., Keppler, J. G., ter Haar Romeny-Wachter, C. C., Boelsma-van Houte, E., van Gent, C. M. (1958) *ibid.* ii, 1207.
— Woodford, F. P., ter Haar Romeny, C. C., Boelsma, E., van Gent, C. M. (1959) *Nature, Lond.* **183**, 47.
Delsal, J. L. (1944) *Bull. Soc. Chim. biol. Paris*, **26**, 99.
Holman, R. T., Hayes, H. (1957) *in* Methods of Biochemical Analysis (edited by D. Glick); vol. IV, p. 126. New York.
Kelsey, F. E. (1939) *J. biol. Chem.* **130**, 199.
Kenny, A. P. (1952) *Biochem. J.* **52**, 611.
Kinsell, L. W., Michaels, G. D., Friskey, R. W., Splitter, S. (1958) *Lancet*, i, 334.
Lewis, B. (1958) *ibid.* ii, 71.
Luddy, F. E., Barford, R. A., Riemenschneider, R. W., Evans, J. D. (1958) *J. biol. Chem.* **232**, 843.
Rosenmund, K.W., Kuhnhenn, W. (1923) *Z. Untersuch. Nahr.- u. Genussm.* **46**, 154.
Sinclair, H. M. (1956) *Lancet*, i, 381.
— (1957) *Brit. med. J.* ii, 1424.
— (1958a) Lectures on the Scientific Basis of Medicine; **6**, 260. London.
— (1958b) *Practitioner*, **181**, 468.
Snedecor, G. W. (1946) Statistical Methods. Iowa State College Press.
Tuna, N., Reckers, L., Frantz, I. D. (1958) *J. clin. Invest.* **37**, 1153.

STAPHYLOCOCCAL ENDOCARDITIS FOLLOWING MITRAL VALVOTOMY
WITH SPECIAL REFERENCE TO COAGULASE-NEGATIVE STAPHYLOCOCCUS ALBUS

LEON RESNEKOV
M.B. Cape Town, M.R.C.P.
MEDICAL REGISTRAR, KING'S COLLEGE HOSPITAL, LONDON, S.E.5

THAT staphylococci can cause subacute bacterial endocarditis was known to Osler (1909), who quoted Lenhartz (1901) on this point. In the Medical Research Council review of 442 cases of this condition (Cates and Christie 1951) only 4 were infected by a coagulase-negative staphylococcus; in fact 94% of all the cases were due to streptococci. But there are more and more reports of endocarditis following mitral valvotomy, in which a staphylococcus (often coagulase-negative) is responsible. I present here 10 cases collected during the past three years.

Case-reports

Case 1.—A man, aged 45, with congestive heart-failure, had a mitral valvotomy in June, 1956: the valve was enlarged with the finger from 0·65 cm. to 2 cm. Heavy calcification was found, and a fair regurgitant stream was felt.

Subsequent fever was at first attributed to a chest infection; but two weeks after operation there were rigors, associated with leucocytosis and red blood-cells in the urine, and blood-cultures yielded coagulase-negative staphylococci. Erythromycin was given for six weeks, but a week after it was discontinued rigors returned, splinter hæmorrhages appeared, and coagulase-negative staphylococci were cultured from the blood. Erythromycin was started again, followed by penicillin and streptomycin for a further month. Thereafter no further rise in temperature occurred, and he was discharged.

Less than a month later he was readmitted. Blood-cultures were positive for coagulase-negative staphylococci, and he was treated with erythromycin, to which 'Albamycin' was later added. After six weeks the drugs were stopped.

In six months he had to be readmitted again. This time

penicillin in high dosage brought the temperature rapidly to normal, and he was discharged after six weeks. Three weeks later rigors returned, and on readmission treatment was started with penicillin, followed by erythromycin. He was discharged well, taking erythromycin; and, 10 months later his blood-culture was still sterile. Clubbing, noticed soon after his first bout of fever, has never gone away. On each of the four relapses coagulase-negative staphylococci have been grown from his blood.

Case 2.—A woman, aged 53, had mitral stenosis with some incompetence, and had had an embolus to the leg. At operation in August, 1957, the mitral valve was found to be heavily calcified, rigid, and much stenosed: only a small anterior split was made and none posteriorly.

She developed fever which did not respond to penicillin. Two weeks after operation there were rigors, and blood-culture yielded *Staphylococcus aureus*. Another embolus to the leg occurred. Thereafter she was readmitted three times with evidence of further infection and in congestive heart-failure. Blood-cultures now yielded coagulase-negative staphylococci. Despite antibiotic treatment the infection could not be controlled and she died fourteen months after operation.

Necropsy showed an acute ulcerative endocarditis with soft friable vegetations. The lumen of the abdominal aorta was largely occluded by thrombus. The right lung showed numerous small abscesses, and an old infarct was found in the right upper lobe—also in the spleen and the right kidney. No significant organisms were grown from the mitral vegetations.

Case 3.—A woman, aged 51. A calcified mitral valve with considerable stenosis and some incompetence was found at operation in July, 1956. Only the anterior commissure could be split.

Two days later fever developed and blood-cultures showed coagulase-negative staphylococci, and on one occasion *Staph. aureus*. Penicillin and streptomycin did not control the temperature, but erythromycin, 1·2 g. daily for seven weeks, did, and she has remained well.

Case 4.—A woman, aged 54, with auricular fibrillation, had been in congestive heart-failure in 1956. At operation in November, 1957, a heavily calcified valve with tight stenosis was found and a small anterolateral and a fair posteromedial split were obtained.

Two weeks later, pulmonary infarction occurred, followed by a swinging pyrexia, splinter hæmorrhages, and enlargement of the spleen. Blood-cultures now yielded *Staph. aureus* in one culture bottle out of three, but subsequently coagulase-negative staphylococci only were grown. Penicillin and streptomycin failed to control the infection, but it responded to erythromycin.

Case 5.—A woman, aged 51, with auricular fibrillation. Mitral valvotomy was performed in May, 1958. There was no calcification of the valve and no regurgitation. A good posteromedial split not exactly in the line of the commissures was done, but only a small anterolateral split. A small degree of incompetence was caused.

In September she attended outpatients, having had two emboli in the legs. She was afebrile, but there was a loud systolic murmur at the apex, and an early diastolic murmur down the left sternal border. The spleen was palpable, and clubbing was now present. Fever developed, and on four occasions blood-culture showed coagulase-negative staphylococci. Penicillin rapidly brought the temperature down, and by the middle of October blood-cultures were sterile. She was discharged taking penicillin by mouth. After six months this drug was stopped, and she has remained well.

Case 6.—A woman, aged 38, with auricular fibrillation had had a cerebral embolus in 1953. At mitral valvotomy in July 1958, no calcification of the valve was found. It was split both anterolaterally and posteromedially with difficulty.

Five weeks later an embolus to the right leg occurred, and thereafter she developed high fever, with jaundice and a leucocytosis. Blood-cultures initially yielded *Staph. aureus*, but subsequently coagulase-negative staphylococci only were grown. Tetracycline did not control the infection, but erythromycin, 2 g. daily, did, and she was discharged well to continue the drug for six months. Since discontinuing the drug, she has remained well.

Case 7.—A woman, aged 41, was twenty weeks pregnant. At mitral valvotomy slight calcification of the valve was found, and anterolateral and posteromedial splits were made with difficulty.

Two months later she had to be admitted with loss of weight, an Osler's node in one finger, clubbing, anæmia, and leucocytosis. *Staph. aureus* was isolated from the blood-stream on one out of nine occasions. She was treated with erythromycin and aureomycin for six weeks and eventually was delivered at term of a healthy infant. Mitral incompetence developed, and congestive heart-failure followed. Her condition gradually deteriorated, and she died ten months after operation.

Case 8.—A woman, aged 26. At mitral valvotomy, on Sept. 11, 1958, a good posteromedial and a small anterolateral split were made. The valve was not calcified.

A week later the temperature rose to 103°F, and blood-cultures yielded coagulase-negative staphylococci. Treatment was started with penicillin, but this was later changed to tetracycline. Blood-cultures later in October were sterile, and she was discharged well to continue tetracycline at home for six months. She has remained well.

Case 9.—A man, aged 44, with auricular fibrillation. At operation in September, 1958, a calcified mitral valve was found. A posteriomedial split was done with difficulty; a Tubbs dilator passed through the anterior wall of the left ventricle obtained dilatation to 4 cm. On the day after operation there was fever, thought at first to be due to pericarditis. Clubbing developed, and an early blowing diastolic murmur was heard. Blood-cultures yielded coagulase-negative staphylococci. Treatment was started with erythromycin, to which novobiocin was later added. At the end of October he was discharged to continue his antibiotics at home for six months, and is now well.

Case 10.—A woman, aged 33. A calcified, stenosed, and incompetent valve was found at operation in September, 1958, and a good posteromedial but tiny anterolateral split were made.

Later there was collapse of the left lower lobe, followed by pyrexia and congestive heart-failure. Blood-cultures yielded coagulase-negative staphylococci. A cerebral embolus occurred next. Penicillin, streptomycin, tetracycline, oleandomycin, and erythromycin all failed to control the infection and she died six weeks after operation. No necropsy was performed.

Clinical Features

It has been suggested (Fleming and Seal 1955) that postoperative endocarditis does not conform to the usual type; but table I shows all the ordinary findings, and my

TABLE I—CLINICAL FEATURES IN THE 10 CASES

—	Case 1	2	3	4	5	6	7	8	9	10	Total out of 10
Pyrexia	+	+	+	+	+	+	+	+	+	+	10
Raised sedimentation-rate	+	+	+	..	..	..	+	+	+	+	7
Leucocytosis	+	+	+	..	..	..	+	..	+	+	7
Anæmia	+	+	..	+	+	+	+	..	+	..	7
Clubbing	+	+	..	..	+	+	+	..	..	..	5
Nodes	+	..	..	..	..	..	+	+	..	..	3
Splinter hæmorrhages	+	..	..	+	..	..	..	..	..	..	2
Emboli	..	+	..	+	..	+	..	+	..	+	5
Proteinuria	+	+	..	..	..	..	..	..	+	..	3
Casts	+	+	..	..	..	..	..	..	+	..	3
Red blood cells in urine	+	+	..	..	..	+	+	..	+	..	5
Change of murmur	+	+	..	..	+	+	+	+	..	..	6
Mycotic aneurysm	..	..	..	..	..	..	..	..	..	..	0
Retinal lesions	..	..	..	..	..	..	..	..	..	+	1
Splenomegaly	..	..	..	+	+	..	..	..	..	..	2

TABLE II—BACTERIOLOGY AND TREATMENT OF THE 10 CASES

Case	Antibiotic cover		Interval between operation and symptoms of infection (days)	Blood-culture			Treatment	Result at present
	Name	No. of days		Organism	Sensitivity			
					Sensitive to	Resistant to		
1	None		2	C.N.S.	S. A. C. E.	P.	E. S. P.	Has had three recurrences, is still on antibiotics
2	P.	10	37	(1) *St. au.* then (2) C.N.S.	E. C. E. C.	P. S. T. P. S. T.	P. T. E. N.	Died
3	P.	7	2	(1) C.N.S. (2) *St. au.*	P. A.	C.	S. P. E.	Well
4	P.	5	13	(1) *St. au.* (2) C.N.S.	C. N. E. C.	T. C. P. S. T.	P. S. E.	Well
5	T.	5	95	C.N.S.	P. S. T. C.	..	P.	Well
6	T.	5	86	(1) *St. au.* (2) C.N.S.	S. T. C. P. T. S. C.	P. ..	.. P. T. E.	Well
7	T.	5	47	*St. au.*	..	..	Au. E.	Died
8	T.	10	10	C.N.S.	P. S. T. C.	..	P. T.	Well
9	T.	5	1	C.N.S.	P. S. T. C.	..	E. N.	Well
10	P.	5	32	C.N.S.	E. C.	P. S. T.	P. S. T. E. Ol.	Died

A. = achromycin, Au. = aureomycin, C. = chloramphenicol, C.N.S. = coagulase-negative staphylococci, E. = erythromycin, N. = novobiocin, Ol. = oleandomycin, P. = penicillin, S. = streptomycin, *St. au.* = *Staphylococcus aureus*, T. = tetracycline.

impression is that clinically our cases differed little from the common subacute bacterial endocarditis due to *Str. viridans*. Both rigors and sweating occurred frequently in the 10 cases. Petechiæ and mycotic aneurysms were not seen, and retinal lesions only once. Enlargement of the spleen was noted in 2 patients, as were Osler's nodes and splinter hæmorrhages. A raised sedimentation-rate, anæmia, and clubbing were the clearest guides to the cause of the pyrexia. A change of heart murmur not explainable by the operation itself—e.g., the development of the murmur of aortic incompetence—was also significant.

The latent period after operation varies. In some cases infection was apparent almost immediately, in others in two to four weeks, and in others after a longer time (up to four months).

These 10 cases, dating from 1956 to 58, occurred among 70 consecutive mitral valvotomies—an incidence of 14%. This is an unusually high figure, for Dalton, Williams, and Atkins (1956) report 3 cases in a total of 150 operations.

Bacteriology

Of the 10 cases, coagulase-negative staphylococci were grown easily in 7.* In case 2, *Staph. aureus* was cultured at first, but coagulase-negative staphylococci later. Similarly, cases 6 and 9 grew *Staph. aureus* followed by coagulase-negative staphylococci. Case 7 yielded a pure growth of *Staph. aureus* on one occasion; subsequently nine blood-cultures were sterile.

In general the organisms were resistant to penicillin, and sensitive in some degree to streptomycin, tetracycline, and chloramphenicol (table II). Most were found sensitive to erythromycin, when tested.

Treatment

Erythromycin seems to have given the best results, for it was used, either alone or in combination, in 8 of the 10 cases. Often treatment was started with another antibiotic, but only when this was changed to erythromycin, did the temperature come down (case 6 for example). Case 5 was the only one which responded fully to penicillin alone.

That treatment should continue beyond the customary six weeks is shown by the ease with which infection recurs. We now recommend antibiotic treatment for at least six months continuously. So far we have seen no harm from long-term treatment using erythromycin up to 2 g. daily, or tetracycline 1 g. daily. The one case successfully treated with intramuscular penicillin was discharged to take penicillin by mouth for six months.

Results

3 patients have died; in 2 death was due to infection uncontrolled by antibiotics individually or in combination. In the 3rd, congestive heart-failure due to valvular damage resulting from the infection was the immediate cause of death.

Case 1 has had to be admitted three times in two years for recurrence of infection; moreover, the heart is large, congestive heart-failure has occurred, and the ultimate prognosis is grave.

Of the remaining 6 cases, it is still too early to draw conclusions except that case 3 has remained well for many months. But the heart has to contend with further damage to the mitral valves, and sometimes to the aortic valves as well; and this may prove important in the future.

Discussion

Staphylococcal bacterial endocarditis is a serious complication of mitral valvotomy.

The mortality-rate has been as high as 66% (Levinson et al. 1950), while 5 out of the 9 patients died in Fleming and Seal's (1955) series. Denton et al. (1957) reported a mortality-rate of 30% in 20 cases of staphylococcal endocarditis following all forms of heart operation. Smith et al. (1958) show a mortality of 28 out of 49 treated cases of septicæmia due to *Staph. albus*, but mitral valvotomy had been performed in only 3 of these. The series had been collected over many years, so modern antibiotics were not always available.

That 3 cases (20%) of our patients died must be considered fairly typical, but in another case the prognosis is considered poor.

* 5 ml. of blood was inoculated into each of three culture bottles of 'Liquoid' broth at the bedside. One bottle was incubated aerobically, one anaerobically, and one in an atmosphere containing 5% CO_2. Subcultures were made every second day. Staphylococcal colonies were tested for coagulase by the slide test of Graves et al., and by the tube method of Fisk. All coagulase-positive staphylococci are referred to as *Staph. aureus* irrespective of the colour of their colonies.

Instead of the three weeks one would expect for mitral valvotomy, these patients stayed in hospital for an average of three months, and have some prospect of chronic ill health.

Diagnosis of the infection following mitral valvotomy is not always easy, and we are loth to make it on fever alone. Coagulase-negative staphylococci are found so often on the skin that we do not rely on positive blood-cultures unless the organism is grown on more than one occasion, and in more than one of three culture bottles. Cunliffe et al. (1943) accept it only if it can be repeatedly isolated from the blood-stream, and if there is only one kind of organism on a pour-plate. *Staph. aureus* is always coagulase-positive and is highly pathogenic.

An interesting problem is posed by cases 2, 3, 4, and 6 where blood-cultures yielded coagulase-positive staphylococci first but only coagulase-negative ones later. A possible explanation is that both organisms were originally introduced and caused the infection, and that the coagulase-negative were more resistant to treatment and persisted.

The source of infection is particularly hard to trace where coagulase-negative staphylococci are responsible for it. This organism may be cultured with ease from persons, and often from much of the equipment in the operating-theatre.

The finger is a possible source when used for the valvotomy, for the glove may be torn while splitting the valve, and there may be a small break in the glove even where no tear is obvious (Fleming and Seal 1955).

Previous *cardiac catheterisation* may add to the risk of infection, but in this series it is not an important factor. Many cases of mitral stenosis have been catheterised at this hospital over the past eight years without a single infection resulting.

Calcification of valve.—In 6 of the 10 cases the valve was heavily calcified. There is a greater risk of tearing the surgeon's glove, infection will then occur easily and will be harder to remove, because the blood-supply is poor. Normally, however, the heavily calcified mitral valve seems very resistant to infection, and only after valvotomy is it infected with ease.

Clearly, the sterile techniques regarded as adequate for other operations are not sufficient for mitral valvotomy, and special precautions are needed.

If possible, the theatre should be one which is used only for heart operations. Comings and goings into and out of the theatre during the operation by nurses, anæsthetists, and onlookers should be kept to an absolute minimum, and ward blankets should not be allowed in the theatre. The article of Blowers et al. (1955) will be found very useful in dealing with possible sources of infection.

When the split is performed digitally the surgeon might lessen the risk of a broken glove by putting a fingerstall of toughened rubber over his gloved finger just before the actual split.

The antibiotic cover we have used (table II) has obviously been insufficient to prevent infection, and should perhaps be prolonged for seven to ten days after operation. The organisms most often concerned are rarely sensitive to penicillin, and broad-spectrum antibiotics should be used: we now think that a combination of tetracycline and chloramphenicol is best. Erythromycin we hold in reserve.

Summary

Of 70 consecutive patients treated by mitral valvotomy, 10 developed staphylococcal endocarditis. 3 patients have died, and the prognosis in another is poor because of the valvular damage.

The infective organisms were coagulase-negative staphylococci alone in 5 cases and coagulase-positive alone in 1. In the other 4, blood-cultures yielded *Staph. aureus* at first but later only the coagulase-negative staphylococcus.

Erythromycin alone or in combination appeared to be the most effective remedy.

The actual source of the infection is often difficult to determine, but special attention must be paid to precautions in the operating-theatre.

Cases 1, 5, 6, 8, and 9 were under the care of Dr. Terence East; case 2 was under the care of Dr. Clifford Hoyle, and cases 3, 4, and 10 under Dr. Samuel Oram; case 7 was under the care of Dr. Eileen Maunsell at St. Giles' Hospital, London, S.E.5. I wish to express my thanks to these physicians for permission to publish the cases. Necropsy on case 2 was performed by Dr. H. K. Mason.

I wish to express my gratitude to Dr. Terence East for helpful criticism and advice in the preparation of this paper.

REFERENCES

Blowers, R., Mason, G. A., Wallace, K. R., Walton, M. (1955) *Lancet*, ii, 786.
Cates, J. E., Christie, R. V. (1951) *Quart. J. Med.* **20**, 93.
Cunliffe, A. C., Gillam, G. G., Williams, R. (1943) *Lancet*, ii, 355.
Dalton, J. C., Williams, B., Atkins, L. (1956) *New Engl. J. Med.* **254**, 205.
Denton, C., Pappas, E. G., Uricchio, J. F., Goldberg, H., Likoff, W. (1957) *Circulation*, **15**, 525.
Fleming, H. A., Seal, R. M. E. (1955) *Thorax*, **10**, 327.
Levinson, D. C., Griffith, G. C., Pearson, H. (1950) *Circulation*, **2**, 668.
Osler, W. (1909) *Quart. J. Med.* **2**, 219.
Smith, I. M., Beals, P. D., Kinsbury, K. R., Hasenclever, H. F. (1958) *Arch. intern. Med.* **102**, 375.

ORAL THRUSH IN INFANCY TREATED WITH NYSTATIN

ROSEMARY D. GRAHAM
M.B. Lond.
MEDICAL OFFICER, LONDON COUNTY COUNCIL

THE antibiotic nystatin, discovered by Hazen and Brown (1951), has proved highly effective against *Monilia* (*Candida*) *albicans*. In Britain, however, little has been published on its use in oral thrush in infants. There follows a report of a clinical trial at two welfare centres in South Kensington where the response to nystatin was compared with the response to the traditional 1% aqueous gentian-violet.

Therapeutic Trial

The trial included all the 55 children under one year, suffering from oral thrush, who were seen in the fourteen months ending Jan. 31, 1959. Of these, 26 were treated with gentian-violet and 29 with nystatin, the preparation being offered to alternate cases. The mouth infection had been discovered on routine examination, and in all but 2 cases the child was otherwise healthy.

Nystatin, supplied as granules in a 24 ml. bottle, was reconstituted as a suspension by the addition of 22 ml. of water. With a calibrated dropper, 1 ml. (100,000 units) of the mixture was given to the infant four times daily with the feeds. At first it was recommended that the antibiotic should be put into the bottle feeds, thus facilitating administration by the mother, but this had to be abandoned because granules stuck to the sides of the container. Thereafter the mother was instructed to insert 1 ml. directly from the pipette into the child's mouth four times daily after the bottle or breast feed. The mother had to understand that nystatin is not soluble in water and that great care must be taken to shake the bottle before each dose, so as to disperse the coarse granules. As the potency of the reconstituted nystatin deteriorates after a week only enough fungicide for a seven-day course was dispensed at a time.

Gentian-violet in 1% aqueous solution was applied by cotton-wool swab directly to the oral mucosa twice daily for a week.

The response is shown in table I. Of the 26 infants treated with gentian-violet, 8 were free from infection

TABLE I—RESULTS OF TREATMENT

Form of therapy	No. of cases	Response		No response	Relapse	Default
		2–7 days	8–14 days			
Gentian-violet	26	8	8	4	3	3
Nystatin ..	29	22	6	0	1	0

TABLE II—AGE OF INFANTS

Age in months	0–1	1–3	3–6	6–12
No. of infants	39	11	4	1

within a week, and a further 8 within a fortnight. 4 did not respond at all, 3 had a recurrence after treatment ceased, and 3 defaulted. Of the 29 treated with nystatin, 22 were free from infection within a week and a further 6 within a fortnight. The mothers said that the white patches on the mucosa disappeared dramatically, often within two days and sometimes after two doses. 1 child relapsed but none failed to respond to treatment, and there were no defaulters.

Some Ætiological Factors

Most of the 55 children were under a month old (table II), the frequency declining throughout the first year of life. The fact that only 6 were born at home is not significant, since this corresponds fairly closely to the home/hospital confinement ratio for London.

Of the 50 children under three months of age, 23 were on the breast and 27 artificially fed. The standard of hygiene was good in all but 2 cases, for the area which the clinics serve has few dirty homes with real poverty.

Most of the cases occurred in the colder months of the year. In only 2 mothers and 1 child was there a history of recent antibiotic therapy—for breast abscesses and a urinary infection respectively.

Dawkins et al. (1958) have shown that pregnancy increases the susceptibility of the vagina to monilia, although infection with this fungus is not the only cause of a vaginal discharge during this period. Of the 55 mothers, 38 gave a history of leucorrhœa since the beginning of the pregnancy whereas of a control series of 55 mothers whose children were free from fungal infection only 20 had had a vaginal discharge.

Discussion

The young inexperienced mother found it easier to administer an antifungal suspension directly by pipette into the child's mouth than to paint the buccal mucosa with gentian-violet. During treatment with gentian-violet, many mothers complained of the staining of the child's mouth, hands, and clothes. Their disinclination to use this form of therapy was probably responsible not only for the defaulters but for some of the failures to respond. In five instances the mothers requested that nystatin should be used in place of gentian-violet as it was cleaner to administer.

Nystatin proved to be non-irritating, non-toxic, and non-allergic and no case was resistant to treatment. The main obstacle to its use was the difficulty of ensuring its even diffusion through the mixture. To get over this Kozinn and Taschdjian (1957–58) used lypholised nystatin in which the antibiotic is still in aqueous suspension but the particles being smaller disperse more readily and provide a larger surface of contact with the lesions. One might perhaps go further and have an emulsion of very finely divided particles which could be added directly to the milk of babies taking the bottle.

It must be stated that at present the cost of a week's treatment with nystatin is about 10*s*., whereas the cost of gentian-violet is a few pence.

Summary

Of 55 infants with oral moníliasis, the 29 treated with nystatin did better than the 26 treated with gentian-violet.

The ease with which nystatin can be administered and the absence of staining make it the remedy of choice.

The present cost of nystatin is the only factor operating against its general application.

I should like to thank Dr. J. A. Scott, medical officer of health for the County of London, and Dr. B. Sharpe, divisional medical officer, Division I, for their permission to conduct and report this trial.

REFERENCES

Dawkins, S. M., Edwards, J. M. B., Clayton, Y. M. (1958) Fungous Diseases and their Treatment; p. 94. London.
Hazen, E. L., Brown, R. (1951) *Proc. Soc. exp. Biol., N.Y.* **76**, 93.
Kozinn, P. J., Taschdjian, C. L. (1957-58) Antibiotics Annual; p. 75. New York.

Reviews of Books

Nutrition and Atherosclerosis

L. N. KATZ, M.D., J. STAMLER, M.D., RUTH PICK, M.D., Medical Research Institute, Michael Reese Hospital, Chicago, Illinois. London: Henry Kimpton. 1959. Pp. 146. 37*s*. 6*d*.

AMERICANS have a reputation for producing big and heavy many-authored books, in which it is often hard to see the wood for the trees. In this little book Professor Katz and his colleagues give a fine catalogue of their trees, for the bibliography takes up 33 of their pages and lists 800 well-chosen references with titles. They are left with only 97 pages for their text, but from these they provide an excellent view of their wood. There are 67 clear figures, some original, but many from other authors, often redrawn and greatly improved. These set out the facts on which the argument is based.

In the U.S.A. the annual incidence of coronary heart-disease is about 1000 cases per 100,000 males aged 45 to 64. The disease is number-one killer of men in the prime of life. Epidemiological findings leave no doubt that conditions of life in general—and patterns of diet and disease in particular—affect the incidence, which is much lower in economically underdeveloped countries than in the United States and other prosperous communities. Ischæmic heart-disease is associated with a metabolic disorder of the blood-lipids, most easily demonstrated by a rise in the serum-cholesterol level. In communities with rich diets, there is a steep rise in serum-cholesterol levels in males between the ages of 25 and 50, but which is small in females until after the menopause. In communities living on simple peasant diets, cholesterol levels are little affected by age, and coronary-artery disease is uncommon.

Experimental work on man has shown that the level of serum-lipids can be profoundly altered by the diet. It is raised by a high intake of animal fats and can be lowered by taking vegetable or marine oils. In general, saturated fatty acids raise the level of serum-cholesterol, and unsaturated fatty acids lower it. The fatty acids containing more than one double bond, notably linolenic, linoleic, and arachidonic acid (the essential fatty acids, E.F.A.), seem to be especially effective in lowering serum-cholesterol levels in man, and most vegetable oils are rich in these acids. But Katz and his co-authors state that it is " particularly premature to conclude that the basic lipid metabolic derangement leading to atherogenesis is a resultant of *primary* EFA deficiency in human diets. The fact is that usual American diets are not low in essential fatty acids—quite the contrary ". A deficiency of E.F.A. " could only be *relative* and *secondary* perhaps to excessive intake of saturated fats, cholesterol, refined carbohydrates and/or total calories ".

The evidence presented emphasises the decisive, but not exclusive, role of diet in the causation of ischæmic heart-disease. Hormonal factors, notably secretion of œstrogens and thyroid hormones, also determine in part the level of blood-

lipids, and affect the incidence. Hereditary factors are certainly important and there are families with high levels of serum-cholesterol and a high incidence of coronary-artery disease. Obesity and hypertension also predispose to it. There is evidence that physical exercise can prevent the rise in serum-cholesterol associated with a high fat intake, and that those who lead physically active lives are less likely to suffer from coronary-artery disease.

The research in the past ten years has led to knowledge which justifies therapeutic actions. A dietary prescription is set out and recommended for patients who have coronary-artery disease, and for those who are particularly susceptible—namely, middle-aged men with two or more of the following derangements: obesity, hypercholesterolæmia, hypertension, diabetes, hypothyroidism, heavy smoking, or a poor family history. Stringent dietary measures are not advised, but rather a general attempt to correct the imbalances and excesses present in diets commonly eaten in America—and also in most European countries, though to a lesser extent. The simple, safe, and reasonable recommendations are:

(1) The curtailment of the custom of adding large amounts of fats to foods by the avoidance of frying, of preparing salad with cheese or sour-cream dressings, and of putting butter, margarine, or cream on vegetables.

(2) For dessert, adherence to the French tradition of serving fruit, instead of the American routine of pies, cakes, and ice-cream.

(3) The correction of obesity by reducing total calorie intake, and especially that from refined carbohydrates, processed fats and spirits, foods which provide " empty calories " with no associated protein, vitamins, or minerals.

(4) The fat intake should be reduced to about 20–25% of total calories, instead of the 40–60% which is so common now. The ratio of unsaturated to saturated fats should be raised. Here common breakfast habits should be changed. The ordinary American breakfast based on bacon, eggs, buttered toast, and creamed coffee gives a huge intake of saturated fats. They should be superseded by breakfasts made up of fruit, whole-grain cereal, and skim milk.

(5) At other meals there should be ample use of vegetables and fruits without the accompanying fat-laden sauces and gravies. This diet should be accompanied by a good hygienic regimen, including regular physical exercise. Such a dietary regimen at first requires constant attention and adjustment by the physician.

Although these recommendations are specifically related in the book to American habits, they can be applied in Great Britain and elsewhere with very minor modifications. The evidence presented by Professor Katz and his colleagues suggests strongly that if the dietary habits of those particularly susceptible to ischæmic heart-disease can be altered along these lines, then the mortality and incapacity caused by this disease will be greatly reduced.

This is a concise, scientific, and practical book which can be strongly recommended, especially to general practitioners and to undergraduate students, who will find it valuable as an example of the experimental methods available for investigation of a chronic degenerative disease. A good index would be useful in future editions.

Enuresis or Bedwetting

FRANKLIN BICKNELL, D.M., consultant physician, the French Hospital, London. London: Heinemann Medical Books. 1959. Pp. 104. 7*s*. 6*d*.

Dr. Bicknell has written (in flowing colloquial style) for doctors, parents, and adults suffering from enuresis. It would be praiseworthy indeed if such a hard task were achieved with complete success, for only knowledge and balance derived from medical training can enable the reader to view the whole subject in proper proportion. There are references to many things which must be mysteries to the layman and which are better left so—" micturating cystograms ", for instance.

For the doctor the book contains much of interest. All aspects of the subject are reviewed, with no less than 167 references, which must have involved painstaking reading. The short chapter on training in early childhood is excellent, and this is followed by a much longer section dealing with the ætiology of enuresis, where the author includes some of his own views amongst many others. He postulates a single primary cause (" slow functional maturation of the higher cerebral centres which control micturition ") with multiple secondary causes, worry being the principal one. A bewildering number of other contributory factors are mentioned, but some (such as enlarged tonsils) are wisely dismissed as irrelevant. The part played by physical abnormalities in the urinary tract is discussed, but there is insufficient guidance on the difficult problem of choosing the right patient for a full genitourinary investigation with cystoscopy.

Treatment is given thirty pages, and there must be few methods ever devised which are not mentioned. But the reader is left with no clear idea of how to tackle the individual case. He is spoilt for choice. If malaga muscatel raisins are really a most valuable treatment, why do we bother with electric alarm devices or psychiatrists?

That the Patient May Know

HARRY F. DOWLING, B.SC., M.D., professor of medicine, University of Illinois, and TOM JONES, B.F.A., emeritus professor of medical illustration, University of Illinois. Philadelphia, London: W. B. Saunders. 1959. Pp. 140. 52*s*. 6*d*.

THIS book is an atlas of diagrams and charts illustrating certain aspects of health teaching and intended for use by the doctor in his consulting-room. It conveys similar information to that once portrayed on varnished fabric wall-charts, but it does so more effectively and attempts to explain, pictorially, a wider range of problems. The diagrams are accompanied by short paragraphs of description on which the doctor may base his explanation while showing the illustration to the patient, and there is a risk that these additions may defeat their own object. The doctor will use his own words in explanation, and the patient looking at the pictu[illegible] may be confused by two simultaneous expressions of the same idea.

Some may say that the presentation is overelaborate, and that the teaching value of the doctor's own drawing is greater, however inaccurately it is drawn on the back of a prescription pad. While the doctor scribbles and talks the listener has just a little more time to assimilate the message conveyed to him. He is denied this when he is confronted with a ready-made, perhaps stereotyped, illustration.

The book may make explanation easier for those family doctors and specialists who find " patient-education " difficult. If so it will stimulate interest in an aspect of practice which receives less attention than it deserves—especially on this side of the Atlantic.

The Differential Diagnosis of Abdominal Pain

Editor: SHERMAN M. MELLINKOFF, M.D., assistant professor of medicine, University of California School of Medicine. New York and London: McGraw-Hill. 1959. Pp. 443. 70*s*.

THIS is a brave attempt to present every possible known cause of abdominal pain: nothing is left to the imagination. Arachnidism is there cheek-by-jowl with metabolic disorders; talc granuloma finds its place with tuberculosis as a cause of chronic peritonitis and therefore pain. The subject is overstretched by the desire to detail every cause, even conditions which do not present primarily or essentially as painful disorders. This, coupled with a lack of emphasis and the method of compilation from summaries of conference proceedings, makes for difficult reading.

A Pocket Book of Proprietary Drugs

ALISTAIR G. CRUIKSHANK, F.R.C.P.E., physician to the geriatric unit, City Hospital, Edinburgh; CORNELIUS STEWART, L.R.C.P., M.P.S. Edinburgh: E. & S. Livingstone. 1959. Pp. 236. 10*s*. 6*d*. (interleaved copy 14*s*.).

THIS new reference book contains details of some 1500 ethical pharmaceutical preparations, and is fully up to date, with mention (in a short appendix) of such recent arrivals as hydroflumethiazide and griseofulvin. It will be very useful in identifying the constituents of strange-sounding preparations; and perhaps in the next edition a cross-index with the *B.N.F.* name and the preparations containing the drug would make it even more useful.

THE LANCET

LONDON 17 OCTOBER 1959

A Plan for Convalescence

THOUGH the working party on convalescent treatment [1] were concerned only with the London area, their report is of far more than local interest. Not only are many of its detailed suggestions equally applicable outside London but it clearly demonstrates the need for a radical change of attitude towards provision for convalescence.

Almost unnoticed, the requirements have altered. Perhaps even more often than before, we still want to free the hospital bed, to provide less costly inpatient care, or (for social reasons) to delay the patient's return to his home; but, in the great majority of cases a stay at a convalescent home after illness is no longer a *medical* necessity. At the time when FLORENCE NIGHTINGALE wrote that " every hospital should have its convalescent branch and every county its convalescent home ", rest, good food, fresh air, and regular hours were obtainable by most hospital patients only in an institution established to supply them; but today this is true only for a small minority. Moreover, country air or sea air (which places 3257 beds in the South East Metropolitan region, compared to 381 in the North West Metropolitan region, which, like Bohemia, has no coastline) are no longer considered a necessity; and modern therapy allows us to place less reliance on " natural " regimens for recovering health. This alteration is reflected particularly in the fall in convalescent beds for children by 35% over the past ten years.

Partly because the medical aspects of convalescence are thus becoming less important, but also because of isolation, lack of medical interest, and the difficulties in providing for the patients who most need it, the convalescent service has become a second-class service—despite the admirable efforts of the King Edward's Hospital Fund and other bodies to give it coherence and encouragement. That (if it exists at all) it should be second-class is obviously wrong; and the working party accept the challenge. Believing that treatment during convalescence should in fact be " more active, more planned and more integrated with other aspects and disciplines of medicine ", they recommend an upgrading of selected homes—which might then be called convalescent hospitals—to give active treatment; and the restriction of the other homes to the " passive " or " holiday " type of case which would then cease to be a responsibility of the hospital service, though they might offer the kind of recuperative holidays which local health authorities have power to provide.

1. The members were: Dr. N. M. GOODMAN (chairman), Dr. R. A. ANDREWS, Captain H. BRIERLEY, Miss I. H. CHARLEY, Dr. JAMES GRAHAM, Mr. B. J. LORD, Commander R. W. PEERS, Miss A. B. READ, Miss M. J. ROXBURGH, and Sir HENRY TIDY.

While the need for " passive " convalescence seems to be adequately met for London, the working party found much evidence of the difficulty in securing proper convalescent care for special medical groups such as asthmatics, diabetics, epileptics, the physically handicapped, cardiac cases, colostomies and ileostomies, cases of skin disease, and special social groups such as adolescents and the aged infirm. " It is particularly in meeting the needs of these special cases that the independent Homes are doing what the National Health Service should be doing for itself, either directly or by contract." Since only some 2000 of the 6500 available convalescent beds in the four Metropolitan regions are in N.H.S. homes, the task of caring for convalescents is even now largely outside the service. Moreover, it is in the contractual beds in the independent homes that almoners find they can most easily place the difficult cases—with the result that these beds are quite fully occupied, whereas N.H.S. homes are a quarter empty. The working party are anxious that convalescent treatment for London should be considered as a whole, and they propose that a joint consultative body should be set up which might stop anomalies such as the closure by one board of a home for a special group for which there may be a big national demand. Better coordination through a " convalescent information bureau " is also advised, and the rationalisation of finance and certain administrative arrangements.

From the labelling of medicines to the experimental provision of day convalescent centres and the use of convalescent homes for preventive and preparatory treatment, the report is full of suggestions (briefly summarised on p. 611). The Ministry of Health rightly commends its recommendations to the hospital authorities.

Viruses Today

NOT long ago the word virus, by itself, was commonly used as a scapegoat for the many pyrexial illnesses uninfluenced by the antibiotic in current favour. Since then there has been a rapid growth of new names—polioviruses, enteroviruses, myxoviruses, arborviruses, and adenoviruses—which signify the great advances that have taken place. This period of rapid development stems largely from the work of ENDERS and his colleagues, who popularised tissue-culture techniques for isolating viruses. Much of the resulting harvest is summarised in the latest issue of the *British Medical Bulletin* [1]; and, although most of the new viruses were first isolated on the other side of the Atlantic, it is encouraging to see how much basic research comes from Britain and the Commonwealth.

Man is affected by three large families of viruses. Firstly there are the enteroviruses,[2] which include polioviruses and the Coxsackie and ECHO groups. This family inhabits the intestinal tract, and its members are not always distinguished from one another so easily as at first seemed possible. The enteroviruses have been related to illnesses ranging from poliomyelitis through aseptic meningitis and myocarditis to summer diarrhœa.

1. *Brit. med. Bull.* 1959, **15**, no. 3.
2. Macrae, A. D. *ibid.* p. 210.

The second family are the viruses of the respiratory tract. These include the myxoviruses causing influenza; the new group of para-influenza viruses,[3] which have been recovered mainly in respiratory diseases of children; the adenoviruses,[4] which can cause influenza-like illnesses and keratoconjunctivitis; and the common-cold virus or viruses.[3] The third family is that of the arboviruses [5]—viruses multiplying in arthropods and transmitted by their bite. This is a large family whose members are distributed throughout the world, mainly (but not entirely) in tropical and subtropical areas. The unravelling of the complex ecology of the arboviruses is a most interesting chapter in biology, and reminds us that their potentiality as pathogens for man and animals is not yet exhausted. In these three large virus families, and also in the pox-virus family, there are many antigenic varieties of virus which point to common evolutionary sources—a situation resembling that found among salmonellæ and pneumococci. On the other hand, many conditions are caused by a virus of which there is only one known antigenic variety—for example, chickenpox and zoster,[6] measles,[7] and trachoma.[8] The new-found ability to isolate, identify, and study these viruses and their relation to man offers many fascinating opportunities.

New methods for culturing different viruses and studying their multiplication include various tissue-culture techniques,[9] cytological, cytochemical, and biochemical techniques,[10] and serological techniques [11]—notably gel-diffusion precipitation and the use of fluorescent antibody. The adaptation of bacteriological methods to the diagnosis of virus diseases is exemplified in the use of the virus-flocculation reaction for polioviruses, described by Prof. WILSON SMITH and his colleagues elsewhere in this issue. Side by side with the application of new techniques to virus research there has been a great advance in our knowledge of virus genetics [12] and of how viruses grow. The discovery that the naked nucleic acid of many plant and animal viruses can initiate infection carries important biological implications.

But there is another side to this picture of rapid advance. It is twenty-six years since the influenza virus was first isolated,[13] and the virus itself celebrated the twenty-fifth anniversary (a little prematurely) by causing the most widespread epidemic since 1918. Fortunately the consequences of the Asian epidemic [14] were in no way comparable with those in 1918; but, although virologists worked as hard as they could in the epidemic, their role was largely that of spectators who were unable to influence significantly the spread of the epidemic. Even in poliomyelitis many doubts remain: the case for killed-virus vaccines has been argued with fervour,[15] although the case for a live-virus vaccine can be put equally strongly.[16] It is encouraging [17] that a live-virus vaccine for measles is now being tested.[14] Vaccines are likely to be most effective in infections caused by a virus with a single antigenic variety; but the situation with the three large virus families is enough to damp the ardour of the most enthusiastic advocate of polyvalent-virus vaccines. Here, what is needed is a wide-spectrum viral antibiotic, and it seems that interferon [18] shows some of the required properties. Interferon, which can now be assayed by a method comparable to that used for bacterial antibiotics,[19] is apparently not toxic at doses which inhibit virus growth; and this encourages the hope [20] that it may be developed for use in virus infections of man.

3. Andrewes, C. H. *Brit. med. Bull.* p. 221.
4. Pereira, H. G. *ibid.* p. 225.
5. Gordon Smith, C. E. *ibid.* p. 235.
6. Downie, A. W. *ibid.* p. 197.
7. McCarthy, K. *ibid.* p. 201.
8. Collier, L. H. *ibid.* p. 231. See also *Lancet*, 1958, i, 993.
9. Westwood, J. C. N. *Brit. med. Bull.* 1959, **15**, 181.
10. Tyrrell, D. A. J., Klemperer, H. G. *ibid.* p. 189.
11. Belyavin, G. *ibid.* p. 193.
12. Burnet, F. M. *ibid.* p. 177.
13. Smith, W., Andrewes, C. H., Laidlaw, P. P. *Lancet*, 1933, ii, 66.
14. Stuart-Harris, C. H. *Brit. med. Bull.* 1959, **15**, 216.
15. Dick, G. W. A., Dane, D. S. *ibid.* p. 205.
16. Sabin, A. B. *Brit. med. J.* 1959, i, 663.
17. *Times*, Oct. 9, 1959.
18. Isaacs, A., Burke, D. C. *Brit. med. Bull.* 1959, **15**, 185.
19. Porterfield, J. S. *Lancet*, 1959, ii, 326.
20. Andrewes, C. H. *Brit. med. Bull.* 1959, **15**, 175.
21. *Lancet*, 1956, i, 621.
22. Hooper, R. *Brit. J. Surg.* 1959, **47**, 71.
23. Jacobson, W. H. A. *Guy's Hosp. Rep.* 1886, **43**, 147.
24. Rose and Carless' Manual of Surgery. London, 1927.
25. Aird, I. A Companion in Surgical Studies. Edinburgh, 1957.
26. Woodhall, B., Devine, J. W., Hart, D. *Surg. Gynec. Obstet.* 1941, **72**, 391.
27. Bradley, K. C. *Aust. N.Z. J. Surg.* 1951, **21**, 241.
28. Rowbotham, G. F., Maciver, I. N., Dickson, J., Bousfield, M. E. *Brit. med. J.* 1954, i, 726.
29. Sartorius, K., Humphries, S. V. *S. Afr. med. J.* 1946, **20**, 734.
30. Lewin, W. *Proc. R. Soc. Med.* 1954, **47**, 865.
31. Rowbotham, G. F. Acute Injuries of the Head. Edinburgh, 1949.
32. Whalley, N. *Lancet*, 1956, i, 805.
33. Whalley, N. *J. Neurol. Psychiat.* 1958, **21**, 229.

Annotations

EXTRADURAL HÆMORRHAGE

EXTRADURAL hæmorrhage of traumatic origin is eminently treatable, provided the diagnosis can be made early and skilled surgical aid is at hand. But the mortality, though varying considerably in the experience of different surgeons, remains distressingly high.[21] Hooper [22] has done a valuable service by reviewing previous reports and analysing 83 personal cases. He points out that the mortality of the condition in Jacobson's series of 71 cases, described in 1886,[23] was 86%, and that no substantial improvement took place in the succeeding forty years despite the advent of neurosurgery; in 1927 von Bergmann was cited [24] as having only 16 survivors in a series of 99 personal cases, so his mortality-rate, too, was 86%. Only two years ago Aird [25] stated that about 50% of patients with this condition died, and the death-rate in several series of cases reported in the past twenty years has either approached or exceeded this figure.[26–28] On the other hand, some neurosurgeons have achieved incomparably better results. Thus Sartorius and Humphreys [29] reported in 1946 that they had had only 1 death in a series of 20 cases, Lewin [30] in 1954 described 46 cases in which the mortality-rate was 21%, while Rowbotham [31] and Whalley [32 33] have also reported that in their experience only about 20% of cases are fatal. The reasons for such wide discrepancies between the results achieved in different centres, in which it can be presumed that methods of surgical treatment are comparable, are not immediately apparent. But, leaving aside possible differences in case selection, the interval between onset and treatment is probably the main factor.

In Hooper's series traffic accidents accounted for 39% of cases, falls for 35%, and blows on the head

for 16%.[22] Extradural hæmorrhages generally follow relatively mild injuries which, though sufficient to cause a skull fracture, often produce an initial period of unconsciousness lasting for less than thirty minutes; the patient rarely loses his senses for more than six hours immediately following the injury. When the source of the bleeding is arterial, due to tearing of the middle meningeal artery or one of its branches, clinical deterioration is rapid; but with arterial and venous bleeding, which is not uncommon, clinical manifestations develop more slowly, and where the hæmorrhage is of purely venous origin clinical manifestations develop still more slowly. Hooper found, in common with many neurosurgeons, that frontal injury tended to give rise to bleeding into the anterior fossa, while a temporal or parietal blow produced a middle-fossa hæmatoma; the rare hæmatomas in the posterior fossa were always due to an occipital injury. Almost invariably the hæmatoma was found directly under the site of the surface injury, and bruising of the scalp was a far more reliable guide to the position of the hæmatoma than was the site of a skull fracture identified radiographically.

About half of Hooper's patients showed the " classical " clinical picture in that an initial period of unconsciousness was followed by a lucid interval, before expansion of the hæmatoma caused further gradual impairment of consciousness. In about a fifth of the patients, however, improvement in the conscious level was only transitory and progressive deterioration followed; while in another fifth the clinical picture was of progressive deterioration from the moment of injury. If operation was not carried out early, drowsiness was followed by confusion, stupor, and finally coma. In the early stages headache was a constant symptom no matter what was the site of the bleeding, and was often unilateral, on the side of the lesion. A considerable proportion of patients with a hæmatoma in the anterior fossa showed unilateral pupillary dilatation on the side of the lesion at a comparatively early stage, but this oft-quoted physical sign appeared late and inconstantly when the hæmorrhage was in the middle fossa (the commonest situation). Signs of contralateral hemiparesis were observed in about half the cases. When the bleeding was in the posterior fossa, neck stiffness, cerebellar signs, and cranial-nerve palsies were often found. If the condition remained untreated, the onset of coma was often accompanied by decerebrate rigidity and later by respiratory failure, owing to distortion of, and consequent hæmorrhage within, the brain-stem. In up to half the cases there is an associated intradural lesion—usually subdural, subarachnoid, or intracerebral hæmorrhage—and at operation it is wise to open the dura so that any intradural blood can also be evacuated. Radiography of the skull is of considerable importance in confirming the clinical diagnosis. A skull fracture crossing the meningeal vessels often gives sufficient confirmatory evidence, but a shift to one or other side of a calcified pineal gland is also helpful. Cerebral angiography, though it too may give findings which are virtually diagnostic, is rarely indicated, because it takes so long: an exploratory burr-hole is generally preferable.

The commonest cause of death in Hooper's cases was respiratory failure before operation. As regards the factors governing prognosis it was found that, although the severity and rapidity of the hæmorrhage and the degree of intradural bleeding were important, the most crucial factor was the patient's conscious level at the time of operation. All patients who were conscious and rational when operated on survived. It was also clear that the survival-rate improved with increasing experience on the part of the surgeon and with improved organisation of the head-injury service in the hospitals concerned.

Clearly, therefore, early diagnosis, immediate admission to a neurosurgical unit, and operation on suspicion are the main means by which deaths resulting from this condition are to be further reduced. Skilled anæsthesia,[34] with hypothermia when necessary, is also important. Hooper suggests that a mortality-rate of 10% should be the maximum in centres with neurosurgical facilities; in his view a substantially higher figure indicates either a low standard of medical education or a poor organisation for dealing with such cases.

MILIARY TUBERCULOSIS

THERE have been few reports on the outcome of treatment of miliary tuberculosis. A report to the Medical Research Council [35] on treatment with streptomycin showed that of 25 patients 14 recovered; meningitis developed in 8. Lawson et al.[36] treated 24 cases (adults and children) with streptomycin; 18 survived, but meningitis developed in 8 during treatment. Of 12 cases treated with isoniazid, with or without streptomycin, none died, and none developed meningitis. Lawson et al. remarked, however, that their series did not include very young children and infants, in whom the prognosis is worse.

Lincoln and Hould [37] have described a follow-up study of 63 children with miliary tuberculosis, treated at the Bellevue Hospital, New York. They remark that between 1926 and 1944 102 children with miliary tuberculosis were admitted to the service and all died, though 3 had temporary remissions. Subsequently, of 9 children treated with thiazosulphone 6 survived, though 3 continued to have active tuberculosis. 29 children were then treated with streptomycin and thiazosulphone; 22 survived, though meningitis developed in 6, one to three months after therapy was started, and of the 28 who survived nine months or longer 13 still showed active tuberculosis. 25 children were given isoniazid: 20 of them were also given streptomycin, and 24 were also given thiazosulphone. Of these, 24 survived; and meningitis developed in none of them during treatment. Lincoln and Hould note that, as more effective drugs have been introduced, the amount of calcification in the primary complex and in metastatic areas such as the spleen has decreased, and clearing of the X-ray evidence of miliary tuberculosis has become more rapid. The remarkable improvement of the outlook with isoniazid treatment is well brought out by these results.

Lincoln and Hould analyse the clinical features of miliary tuberculosis in 165 children, including those seen before the streptomycin era. Of these 165, 164 had fever, and in 46 it was the only symptom. The spleen was enlarged in 78. Tuberculin tests were positive in 150. Choroidal tubercles were found in only 21. This contrasts strikingly with the findings of Illingworth and Lorber [38] who detected choroidal tubercles in 70 of 99 children with X-ray evidence of miliary tuberculosis. Undoubtedly a careful search for choroidal tubercles,

34. Bell, K., Clarke, P. *Lancet*, 1956, i, 969.
35. Report to the Medical Research Council. *ibid.* 1950, i, 841.
36. Lawson, J. H., Lees, A. W., Allan, G. W., McKenzie, P. *Brit. med. J.* 1954, ii, 839.
37. Lincoln, E. M., Hould, F. *New Engl. J. Med.* 1959, **261**, 113.
38. Illingworth, R. S., Lorber, J. *Arch. Dis. Childh.* 1956, **31**, 467.

after proper sedation, and with the pupils dilated, is well worth while.

The final diagnosis depends largely on radiology, but in early miliary tuberculosis radiographs may not show the characteristic mottling of the lung fields. Emery and Lorber [39] described how miliary tuberculosis in the lungs had been diagnosed by a panel of radiologists in only 28 of 52 cases where evidence of miliary spread had been found at necropsy. In doubtful cases the diagnosis must be made on the whole clinical picture, and in particular on the finding of choroidal tubercles.

NUTRITION AND INFECTION

AN association between undernourishment and epidemic infections is often taken for granted. Certainly, history has many records of famine and pestilence apparently enhancing each other's contribution to human suffering. But these situations are always complex interactions of many variables—such as overcrowding, lowered morale, breakdown of public-health arrangements, and refugees in flight. In man, therefore, it is impossible to measure the influence of some form of undernourishment on any particular infection, although there may be little doubt that it contributes something. This whole problem clearly fascinates nutritionists, epidemiologists, and microbiologists. It cannot be said, however, that their published work on the subject blinds the reader with the light of revelation. We owe a considerable debt, therefore, to Dubos and Schaedler, not only for their original experimental work, but for undertaking yet another review [40]—a review which brings at least some order and perspective.

Determination to reduce the number and influence of variables in work on nutrition and infection has naturally led to studies in laboratory animals. Unfortunately many of these studies bear the mark of having been done by nutritionists or microbiologists with imperfect understanding of each other's discipline. It makes a good beginning to realise that the terms "nutrition" and "infection" are too wide and too vague to permit of any generalisation. For example, although riboflavine deficiency in chicks decreases the severity of *Plasmodium lophuræ* infections,[41] and although there is evidence that other vitamin deficiencies may protect certain hosts against infections with particular parasites and viruses, it would be seriously wrong to assume that the same nutritional deficiencies will protect the same hosts against other infective agents or other hosts against the same infective agents. The sad fact is that we must confine ourselves to a number of propositions. For example, Howie and Porter,[42] examining six diets used to rear laboratory mice, showed that those which proved best for growth and reproduction were not those most favourable for resistance to infection with salmonella or the tubercle bacillus; and this negative generalisation is now supported by the work of Boyden and Andersen,[43] who studied experimental tuberculosis in the guineapig, and by that of Dubos and Schaedler.[44] Boyden and Andersen [43] also described suggestive evidence that greenstuffs available in the springtime in Denmark increased the resistance of guineapigs to tuberculosis through the agency of substances other than vitamin C and other known nutrients. This suggestion that natural material contains an unidentified anti-infective substance is a challenge to biochemists—a challenge also implicit in Schneider's classic work.[45] Schneider showed that a wheat and milk diet contains an unidentified factor which protects mice against salmonella infection; and he has also offered another possibly valid generalisation—namely, that an active nutritional influence on infection may be obscured by a stronger hereditary one operating either in the host or in the parasite.

Readers of Dubos and Schaedler's review will find a good deal that is encouraging to further work. Cobalt increases the resistance to pneumococci and staphylococci of mice receiving excessive amounts of manganese in their diet. [46] Diets deficient in biotin or pantothenate may, it seems, reduce resistance to *Corynebacterium muris* infections in rodents. Investigations by Dubos and Schaedler themselves [44] have shown that a good many experimental infections of mice (with tubercle bacilli, staphylococci, and klebsiellas, for example) are more rapidly lethal to animals given semisynthetic diets and 5 or 8% casein than to those given the same diets with 20% casein. The balance of aminoacids as well as the total protein intake was evidently significant in these experiments. Moreover this kind of dietary influence may be demonstrable after giving the experimental diet for as short a period as two days in two consecutive weeks. In the past many potential workers may have been deterred by knowing that some dietary influences did not become apparent except in animals whose parents had also been fed on the experimental diets.

THROMBOPHLEBITIS FOLLOWING DENTAL EXTRACTION

Two cases of pulmonary infarction after dental extractions have been reported by Adams and Hudgins.[47] In each case the infarction resulted from cervical thrombophlebitis—a condition believed to cause pulmonary infarction only rarely—and in each case, although there was extensive periodontal disease and advanced caries, the extractions had been performed under local anæsthesia. Swift [48] collected 49 cases of neck infections between 1903 and 1940. In all but one of the fatal cases teeth had been extracted, and local or block anæsthesia was used in all these fatal cases. Dental extraction may also be followed by retrograde thrombophlebitis of the facial vein, with spread into the ophthalmic vein or cavernous sinus.[49]

These may be uncommon complications of oral surgery, and, with antibiotics, they are now more readily treated; but they are still dangerous. An important factor determining these complications may be local anæsthesia in cases where dental sepsis is already present. In such cases general anæsthesia is greatly preferable; but the sepsis may not be detected unless the teeth are examined radiographically, and, with sepsis present, much more than the usual amount of local-anæsthetic agent may have to be given, thus possibly enhancing the risk of infection spreading. Where multiple extractions are to be undertaken, preliminary radiographic examination and skilled general anæsthesia should be provided, particularly for diabetics and patients with other systemic diseases which may predispose to the spread of infection. If a nerve-block is to be applied, injection of the local anæsthetic should be preceded by aspiration to ensure that the needle

39. Emery, J. L., Lorber, J. *Brit. med. J.* 1950, ii, 702.
40. Dubos, R. J., Schaedler, R. W. *J. Pediat.* 1959, **55**, 1.
41. Seeler, A. O., Ott, W. H. *J. nat. Malaria Soc.* 1946, **5**, 123.
42. Howie, J. W., Porter, G. *Brit. J. Nutr.* 1950, **4**, 175.
43. Boyden, S. V., Andersen, M. E. *Acta path. microbiol. scand.* 1955, **37**, 201; *ibid.* 1956, **39**, 107.
44. Dubos, R. J., Schaedler, R. W. *J. exp. Med.* 1958, **108**, 69.
45. Schneider, H. A. *Ann. N.Y. Acad. Sci.* 1956, **66**, 337.
46. Hitchings, G. H., Falco, E. A., Sherwood, M. *Fed. Proc.* 1949, **8**, 207.
47. Adams C. W., Hudgins, J. M. *J. Amer. med. Ass.* 1959, **170**, 412.
48. Swift, A. G. *N.Y. St. J. Med.* 1940, **40**, 779.
49. Nathanson, I. G. *Oral Surg.* 1953, **6**, 1405.

has not entered a vein. But local anæsthesia, whatever its importance, is not the only factor determining spread of infection; for excessive rocking of a pyorrhetic tooth during extraction has been repeatedly shown to result in transient bacteriæmia, irrespective of the type of anæsthesia.

YOUTH IN MODERN SOCIETY

ADULTS, if they are to understand young people, must first make a full and often painful self-appraisal, from which the majority shrink. There is no such thing as a "youth problem" in isolation; but there is a network of problems involving both young and older people: the care of children and the maintenance of stable family life, the objectives of by far the largest part of social work, are inextricably interwoven.

Miss Jane Rowell, in her presidential address [1] to the annual conference of the Association of Children's Officers at Folkestone on Sept. 30, identified several factors which are widely held to contribute to the unrest and confusion characteristic of modern industrialised society. Children and young people are especially exposed to the stresses created in an urban culture; and many of their problems and difficulties of adjustment, including much delinquency, are attributed to this cause. These anxiety-disposing factors may be listed as a multiplicity of choice, increasing geographical mobility of families, greater social mobility between the various income-groups, the high speed of social and technological changes, a confusion of ethical values, a general climate of public opinion disposed to question the validity of traditional beliefs and standards of behaviour, and increased purchasing power and comparative economic security. While social scientists may agree that these forces exist, they exert a demoralising influence not solely on young people: their impact on adults is possibly greater, and the confusion of adult moral standards may lie at the root of much juvenile disorder. The centre of attraction should be, not the psychology of aggressive teddy boys, but the causes of breakdown of family life and parental care. We might ask ourselves two crucial questions: why are there so many ineffective parents, and what aspects of the social structure are particularly inimical to young people's stable development? It is not so much "Why are there so many bad boys?" as "Why are there so many bad homes?".

The failure of much contemporary social work can be traced to inability to grasp the implications of these questions. Social workers are in the main concerned with the individual and his personal problems and insufficiently with the group to which he belongs and which moulds his attitudes and behaviour. Child-guidance clinics, as those working in them recognise, may help individual children to cope with some of their difficulties, but cannot often touch the root causes of their unrest. Until we learn to examine the mould and matrix we shall continue to have the puzzling paradox of more and more delinquency side by side with more and more social-work care; for while the individual may be helped to overcome some of his problems the rising generation is already learning to repeat them.

One of the questions which Miss Rowell suggested we could usefully ask ourselves was why the delinquency-rate is so much higher for boys than girls. Boys are more than ten times as likely as their sisters to commit offences. We do not know for certain why this should be so, but can make an enlightened guess. It very probably reflects the different role of women in our society and the different ways in which girls are prepared to carry out this role. The training of girls from a fairly early age is directed mainly towards marriage and home-making and the performance of tasks which are both personally and socially stabilising. Boys on the other hand are encouraged to be adventurous, ambitious, and self-seeking, and traditionally in nearly all classes are given greater freedom of movement and treated with more indulgence. Parents in the middle-income group, for instance, may stint their daughters so that their sons may have boarding-school education. Working-class mothers will demand that their girls undertake considerable household chores, while they are inclined to let their boys run wild in the streets. Nevertheless young people who break the law or by their behaviour in other ways become the focus for anxiety are still comparatively few. The vast majority —well over 90%—of all young people grow up without undue strain or disorder. Most of them can sustain the rapid pace of change, the complexity, and the confusion of modern life—probably with less difficulty than their seniors, for youth is more adaptable, resilient, and unafraid. The minority who fail often do so because their elders have failed them. For example, to obtain the right sort of work may lead to frustration and rebellion unless society provides temporary stabilisers: here churches, youth clubs, and voluntary organisations can exert an immense influence. Adolescent boys need status and reassurance, and opportunities to demonstrate to themselves and to others their powers and qualities if they cannot find the opening they seek. If work proves unsatisfying or if the rigidity of the apprenticeship system thwarts their ambitions, achievement in sport and recreation may give them the reassurance they need.

The so-called youth problem cannot be solved punitively, nor can it be more than mitigated by social services. It can be resolved only by modifying the social structure in such a way that parental responsibility is reinforced and the status of youth recognised. Condemnation is easy and originates in fear. Knowledge and sympathy are the basis for sound and sensible policies. But before these can be put into effect more research is needed in the borderland where sociology and psychology meet. A better understanding of the way in which human personality is conditioned by the position an individual occupies in the social structure will allow us to offer the ferment of youth more satisfying and satisfactory outlets than misdemeanour.

1. See *Times*, Oct. 1, 1959.

GRANULOMAS

AN apparently fatal syndrome in children has been reported by Bridges et al.[1] In each of four cases, all in males, the disease began in infancy with enlargement of the cervical, and occasionally the axillary and inguinal, lymph-nodes. Abscess and sinus formation followed, with fever, weight loss, and anæmia. A rash appeared on the face; in its mildest form this resembled seborrhœic dermatitis, and when more severe it had an eczematoid character. As the disease progressed, hepatosplenomegaly and widespread lymphadenopathy developed. Treatment had little or no effect on the illness, which lasted for up to five years. Pulmonary involvement apparently heralded the terminal phase. The lymph-node suppuration then

1. Bridges, R. A., Berendes, H., Good, R. A. *A.M.A. J. Dis. Child.* 1959, **97**, 387.

retrogressed, and the systemic signs became prominent; death ensued within a year.

Investigation showed a neutrophil leucocytosis and a constant increase in the gamma-globulin, with levels up to 5·0 g. per 100 ml., and a less striking rise in the α_2 and β globulins. At biopsy the characteristic lesions were granulomas at numerous sites, especially the lymph-nodes, liver, spleen, lung, and skin. Histologically, the granulomas resembled tubercles, consisting of rings of mononuclear cells surrounding an area of homogeneous eosinophilic material; giant cells of Langhans type and plasma cells were also present. Bone-marrow aspirates from each child showed plasmacytosis, but no morphologically atypical cells were found.

Extensive studies failed to reveal the cause; but Bridges et al. suggest that the disease " could represent an alteration in immunological response turned against the reticuloendothelial system whose functional and anatomical alteration and eventual destruction results in the clinical picture presented ". The defect may be hereditary; for one child had a remarkable family history, in that at least two males in each of the preceding three generations had died in infancy with an inflammatory lesion of the neck, thought in some to be scrofula.

The distinction of different forms of granuloma one from another and from other types of lesion is often far from easy; and Walton [2] has done a service by carefully studying the nature of non-healing granulomas of the nose. Walton finds that these consist of three separable entities: (1) reticulum-cell sarcoma; (2) Wegener's granulomatosis; and (3) classical malignant granuloma. Walton says that in Wegener's granulomatosis nasal ulceration is linked with similar granulomatous lesions in the trachea and bronchi and there are also widespread granulomatous and vascular lesions elsewhere in the body, whereas in classical malignant granuloma the local ulceration is paramount and there are no disseminated lesions. (Prompt recognition of malignant granuloma is important if Singh et al.[3] are correct in their suggestion that early treatment with steroids and local irradiation may be of value.)

A granulomatous reaction may be elicited by many different substances, including bacteria, viruses, fungi, and protozoa, silica, cholesterol, and other inorganic and organic substances. In other disorders, such as rheumatism, sarcoidosis, Wegener's granulomatosis, histiocytosis X, and, perhaps, Hodgkin's disease, the causal agent is unknown. Discussing granulomatous inflammation, Forbus,[4] having noted its ætiological diversity, pointed out that " the established facts relative to the morphology and function of the cells of the reticulo-endothelial system suggest that there may be in this great variety of etiologic agents something, a specific factor or pathogenic potential, that is common to all "; and this common factor may be a hypersensitivity response. In Wegener's granulomatosis [5–7] there is good evidence that the disseminated granulomas are caused by a hypersensitivity reaction,[8] though the causal antigen—sometimes a drug—is in most cases unidentified. Teilum [9] suggested that in sarcoidosis the lesions had a common allergic origin. The long incubation period of beryllium granulomas suggests either a slow chemical action or a sensitisation phenomenon.[10] The giant-cell granulomas in Whipple's disease may be due to a tissue hypersensitivity to mucoproteins.[11] Giant-cell granulomas are the hallmark of severe drug reactions,[12–14] and similar lesions, with or without giant cells, have been produced by the injection of antigens into sensitised animals.[15 16] Shelley and Hurley [17] have shown that the granulomatous skin reaction which developed in a minority of people using deodorant sticks containing zirconium was the direct result of a specific hypersensitivity to zirconium. This is the first time that the introduction of extremely small amounts of a pure substance has produced an allergic epitheloid granuloma in man.[18] Shelley and Hurley suggested that a search for minute sensitising agents may lead to the discovery of the cause of granulomatous diseases of hitherto unknown origin.

2. Walton, E. W. *J. Laryng.* 1959, **73**, 242.
3. Singh, M. M., Stokes, J. F., Drury, R. A. B., Walshe, J. M. *Lancet*, 1958, i, 401.
4. Forbus, W. D. *A.M.A. Arch. Path.* 1955, **25**, 427.
5. Wegener, F. *Verh. dtsch. path. Ges.* 1936, **29**, 302.
6. Godman, G. C., Churg, J. *A.M.A. Arch. Path.* 1954, **58**, 533.
7. Walton, E. W. *Brit. med. J.* 1958, ii, 265.
8. Walton, E. W., Leggat, P. O. *J. clin. Path.* 1956, **9**, 31.
9. Teilum, G. *Amer. J. Path.* 1948, **24**, 389.
10. Sterner, J. H., Eisenbud, M. *A.M.A. Arch. industr. Hyg.* 1951, **4**, 123. See *Lancet*, Aug. 15, 1959, p. 118.
11. Puite, R. H., Tesluk, H. *Amer. J. Med.* 1955, **19**, 383.
12. Harcroft, W. S. *Canad. med. Ass. J.* 1944, **51**, 23.
13. More, R. H., McMillan, G. C., Duff, G. L. *Amer. J. Path.* 1946, **22**, 703.
14. O'Brien, O. J., Storey, G. *Brit. med. J.* 1954, i, 792.
15. Goddard, J. W. *Amer. J. Path.* 1947, **23**, 943.
16. Goldgraber, M. B., Kirsner, J. B. *A.M.A. Arch. Path.* 1958, **66**, 618.
17. Shelley, W. B., Hurley, H. J. *Brit. J. Derm.* 1958, **70**, 75; *Henry Ford Hosp. med. Bull.* 1958, **6**, 279.
18. See *Lancet*, 1958, i, 1164.
19. Edwards, F., McKeown, T., Whitfield, A. G. W. *Brit. J. prev. soc. Med.* 1959, **13**, 51, 59.

FITNESS FOR WORK IN ELDERLY MEN

IF this country is to carry the steadily increasing economic burden of the aged, as many men as possible should continue in productive work after the age of 65. This would undoubtedly please many of the elderly themselves, for the large fall in income on retirement may cut a man off from his former associates and lead to a feeling of frustration and uselessness. How many would be fit to continue working after 65 is another matter, and little is known about it.

Edwards, McKeown, and Whitfield [19] have investigated this question. With the help of a team of general practitioners they inquired into the health of a representative sample of men over 70 in Birmingham. The main disabilities among these men were due to bronchitis, ischæmic heart-disease, and arthritis. Hypertension, hernia, and peptic ulcer were also common but caused much less disability. The prevalence of all these disorders except bronchitis was unaffected by social class, and only arthritis showed an increased frequency with age.

Disability for work naturally varies with the nature of a man's occupation. Two-thirds of those in social class I (professional) were considered fit for whole-time work, and a third were actually working. Only a fifth of those in social class V (unskilled) were fit for work, and most of these were still in employment. A fifth of those in social class I and three-fifths of those in social class V were unfit for any kind of work; a very large part of this class difference was due to chronic bronchitis. Irrespective of social class there were nearly as many more men over 70 fit to work as were actually in employment.

The men were also questioned about their chief pleasures and complaints. Gardening was the largest single source of pleasure and poor health the chief complaint. The majority had a good appetite and enjoyed their food. Two-thirds of them were under some sort of medical supervision, but only 5% required injections, dressings, or drugs. 7% needed help with washing, dressing, and feeding. The only service needed by these men on a large scale was domestic help, which was required by about half.

Special Articles

FACTORY IN A WARD

S. D. COLLINS
S.R.N., R.M.N.
CHARGE NURSE

S. J. FYNN
A.H.A.
DEPUTY SECRETARY/FINANCE/SUPPLIES OFFICER

FRANK MANNERS
R.M.N.
CHARGE NURSE

ROGER MORGAN *
M.B. Lond., D.P.M.
LATE REGISTRAR

GOODMAYES HOSPITAL, ILFORD, ESSEX

EIGHTEEN months ago we started factory work in a ward of chronic male patients. We wanted to provide activity for more of our patients than could be influenced by traditional hospital occupations; we hoped that payment according to output would encourage the difficult ones; and we could think of no other activity so well suited to our limited staff. Our hopes have been fulfilled and factory work has spread first to our sister ward, then to a workplace, and more recently to three further wards (two male and one female), occupying altogether about 150 patients.

THE WARD AS IT WAS

The ward contained 36 refractory, chronic, deteriorated patients. It had always had a locked door, and, though the rigid discipline of pre-war days had been relaxed, it was still a ward where patients needed direction and some display of authority.

Patients

The patients ranged in age from twenty-seven to eighty-one, but only 5 were over sixty. Only 1 had been admitted during the previous year; 28 had been in hospital for more than five years, and of these 11 had been there for more than twenty years. All except 3 were schizophrenic, 2 were psychopaths with disturbed schizoid periods, and 1 was manic-depressive. 3 patients (all schizophrenic) had had leucotomy. 7 were receiving chlorpromazine, but there was no other active treatment, apart from sedation which was used only to control violent behaviour.

A third were reliable enough during their stable phases to be allowed to go freely in and out of the ward, but all had to be confined at times. A further 15 were usually well enough to be taken out under escort, but the remaining 9 were virtually never allowed outside the ward and its adjoining garden. 24 were certified and 12 were voluntary patients.

Only a quarter were capable of coherent conversation; a further 7 could reply to simple questions, which had often to be repeated. 7 worked in one of the hospital departments when well enough, 10 were reliable ward-workers with enough initiative to get on without constant supervision, a further 11 would polish or dust with a nurse in attendance, and the remaining 8 could not be induced to do work of any kind.

Staff

Our complement of nurses has remained unchanged. It consists of a charge nurse, a staff nurse, a student nurse, and an orderly on each of the two shifts. The doctor and one charge nurse had worked there for fifteen months and the other charge nurse for six months.

SOME EARLY PROBLEMS

In December, 1957, the first few patients were introduced to the splitting and sorting of mica, and 2 of them departed to bed in extreme agitation. Soon, however, both patients and staff became more confident. At first, supervision had to be close and practically continuous. We worked through the problems of book-keeping and accounting, storage, making contacts and developing working relationships with people in the outside firms, running out of raw materials until some system of regular delivery was worked out, making and scrounging simple apparatus such as jigs and containers, getting the ward lighting improved, paying the patients for work done before the payment for it had come in from the firms, and keeping going all the life and administration of the ward that had previously occupied the whole day.

Space and Time

One of our main difficulties is space. We have not sacrificed any beds but by rearranging stores have freed quite a large room to take all our materials, next to the ward dining room, where the work is done. The trouble of stowing the work away has to be endured twice a day, but things never have long enough to get in a mess. The patients work for two hours in the morning and two hours in the afternoon. We had intended that they should have Thursday as well as Saturday afternoon off, but mid-week visitors are rare and the patients mostly prefer to work all day on Thursday. They have occasionally willingly worked over the weekend, too, on a rush order.

We should perhaps emphasise that no patient is forced to work. But in our opinion it is both possible and desirable to offer patients inducements to work.

Earnings and Output

When the job lends itself to this we pay the patients according to piece-rates; but some jobs do not, and then we have to estimate the patients' share of the output achieved by a team. Allowance is made for any patient who achieves less in a disturbed phase of his illness. Ordinarily we deduct and keep about 10% of the earnings. This provides an insurance against work being rejected by a firm after the patients have been paid, and also a fund for comforts and amenities for the ward as a whole. Also, a guaranteed minimum wage can be paid while patients are learning a new job.

The patients have split and sorted 15 cwt. of mica, made 150,000 boxes and 10,000 carrier bags, stuck 44,000 labels, painted several hundred toy horses, and counted and bundled millions of punched-out cardboard shapes from which boxes are later made. In the first year, the ward earned £290, of which £270 was paid to the patients and £20 retained. The weekly wage varied from 2*s.* to 10*s.*, which was considerably less than we expected; but to achieve the rate of output required by the firms, we have to put more hands on a job, for each patient's output is comparatively low. The low earnings have avoided a difficulty that we feared—namely, that vital workers might be attracted away from the hospital departments. The firms pay the same rates to us as to the other outworkers they employ.

Administration

A subcommittee appointed by the physician-superintendent holds weekly meetings to discuss policy. The chairman is the consultant in charge of factory work, and there are representatives from each nursing administrative office, the deputy secretary, the sister or charge nurse on duty from any ward, the staff nurse in charge of the workplace, and the junior doctor. The head occupational therapist and the senior psychiatric social worker attend whenever they wish. The day-to-day running of the work within the ward is decided at the doctor's routine daily visit. Communications with outside firms go through the deputy secretary, who also handles the money in his capacity as deputy finance officer.

HOW THE PATIENTS ARE NOW

During the first year, the best 6 of the 36 patients left the ward. Comparisons can only relate, therefore, to the remaining 30 patients.

They are all schizophrenic except for 1 schizoid psychopath, and, since they have become a year older, one might expect further slight deterioration.

2 patients have been promoted to work outside the ward. 3 patients are doing ward work. 2 patients have been found

* Present address: Severalls Hospital, Colchester, Essex.

too deteriorated to do any work at all. The remaining 20 do factory work.

Before the factory work began, the charge nurses, using Baker and Thorpe's scales, had assessed the patients' behaviour.

Ten aspects of behaviour are considered and rated on a 5-point scale on which 0 represents normality and 4 indicates the greatest deviation from normal. Each patient's total score, therefore, may be anywhere between 0 and 40 and the higher the score the greater the deterioration.

A reassessment of the patients after a year's factory work showed the following changes:

The average patient sleeps better at night (the average rating changes from 1 to $^1/_2$), he is more retarded ($^1/_2$ to 1), less restless ($1^1/_2$ to 1), continues to eat normally, talks rather less (1 to $1^1/_2$), remains fairly tidy as before, works with less supervision ($2^1/_2$ to $1^1/_2$), is still incontinent occasionally, is much less aggressive (2 to $^1/_2$), and slightly more friendly ($2^1/_2$ to 2).

According to these ratings 24 patients have improved and 6 are worse. The ones who have improved have changed their average rating from $12^1/_2$ to 8, and naturally tend to follow the same changes as the ward as a whole, which their own improvement determines. They share the general tendency to a slight increase in retardation, probably due to more extensive use of chlorpromazine which is now being given to 18 instead of 5 of the improved patients. The 6 patients who have deteriorated further during the year have changed their average rating from 10 to 11. It is interesting that their average rating was better before the project began than those who have improved. Their sleep has become only average instead of better than average; they also are slightly more retarded (4 instead of 2 now receive chlorpromazine). Their tendency to speak less is so obvious that it has influenced the result for the whole group; their work is improved; they never were aggressive like the other patients (1 instead of $2^1/_2$), so their improvement to the $^1/_2$ which is the average is less striking; and they have become slightly more withdrawn and unfriendly.

In short, while the patients who have improved during the year were the more restless, aggressive, and negativistic ones, those who have deteriorated are those who from the start have been more passive, empty, and inert and have lacked the resources that factory work can harness to productive ends, though they showed up better originally under more restrictive conditions.

But these figures cannot convey the atmosphere of two busy rooms which buzz with purposeful organised activity, where there are few patients sitting idly about, and the energetic ones are too fully occupied to have time to pick quarrels with each other. Casualties from fights have fallen for the last four periods of six months from 19 to 3.

After nine months of work the ward was opened. Though a few patients have run away, they have been fetched back, or more often have returned of their own accord. No patients had to be transferred from the ward before it could be opened and such a step could not have been taken nine months earlier.

WORK AS THERAPY

In working for outside firms, our patients are submitting themselves to responsibility and discipline. The nurse may direct matters of detail, but it is the firm which wants the order returned by a certain date, and which is going to reject unsatisfactory work. We deliberately remind patients of the outside interest in what they are doing. So as to foster ties with reality, we explain and discuss what the things made are going to be used for.

Payment by output seems to be an effective incentive even to chronic patients. There is a tendency in mental hospitals to expect patients to work willingly for token payment and this may emphasise to them their inferiority and general lack of worth. A number of patients faced with this situation give up all intention of occupying themselves in any way. But when the convention of outside life is restored, they take up work again fairly readily and quickly develop enthusiasm for it. The world of the ward reflects the bigger one outside fairly accurately; for we also have our idle rich, and a few shillings a week are little incentive to a man with private means, such as a pension of 10*s*. a week.

All the jobs we have had could be broken down into stages of varying complexity. This breaking down is something that happens to some extent automatically when several patients share one job; but we owe our grasp of its importance to the head occupational therapist, who has often laid stress on it. With patients of varying capacity, and jobs with stages of varying complexity, there are reasonable prospects of a happy union. In the early stages we had many surprises from the patients whose capacities in this type of work often bore little relation to their abilities in other aspects of ward life. Perhaps because our patients are quite severely deterioriated, it is always difficult to find patients fit enough to carry out the more complex stages of a job. But when the best patients are extended to their limit this tendency is passed down the line to the most deteriorated. On the rare occasions when a job has been too simple, the patients have soon become bored and uninterested and output has fallen.

Most of the work done has been in batches, with the result that there has been a change every few days or weeks. A label has to go in a different place, or a box is a different shape with different colours and words on it. Usually, therefore, we have not had to worry about the possible harm from the monotony of endless repetition. And a job does not seem to be so simple and repetitive to the deteriorated psychotic as to the normal person.

Probably for this reason, we have found that our patients do master a task very slowly. It takes them quite a long time to reach the required standard of work at all; a long period follows when their work fluctuates in quality; and long beyond this time their speed of performance will continue to improve. The whole process often takes several months.

ADVANTAGES OF WARD AS WORKPLACE

We are treating patients who are so deteriorated that in the present state of our knowledge there is no prospect of discharging them from hospital. Our aim has been the simpler one of employing some of our underemployed (including hitherto unemployable) patients and substituting simple repetitive work for what someone aptly described as simple repetitive sitting.

The result of keeping the work in the ward has been to improve the attitude and working conditions of the staff. Opportunities for a constructive relationship with patients have been created, and the custodial function has largely given way to a therapeutic one. For the nurses, interest and increased activity have brightened a working day that tended to be drab, monotonous, and demoralising. Scope for ideas, invention, and organisation has drawn out their talents. The doctor has had a medium through which to get to know individual patients better and hence to prescribe other active treatment and observe their reaction to it. The interest shown by people outside the ward is stimulating and parties of visitors from within and without the hospital make a tremendous difference to the attitude of those working in such a ward.

Any scheme for work outside the ward cannot catch the enthusiasm of the nurses or doctors in the same way. If some of the nurses accompany the patients to work,

this splits the staff and creates difficulties. If others take over, control is lost, misunderstandings arise, uneasiness sets in, the nurse wastes his detailed knowledge of his patients and resents losing the most interesting, therapeutic, and rewarding side of his work.

When the work is done in the ward more patients can be drawn in. It is difficult for a lazy, apathetic, stubborn, or openly hostile patient to hold out for month after month, when taking part will earn the nurses' approval and a place on the pay-list at the end of the week. Often a patient will refuse to start work at the regular time, but will become amenable to persuasion perhaps only a few minutes later. Such a delay cannot be tolerated where a party of workers has to be sent off under supervision to a separate place. The deteriorated schizophrenic does not easily form relationships with other people; but in the ward he can work under the guidance of the nurses he knows.

We recognise that many patients gain from getting out of the ward and enjoying a change of environment, and we agree that " going to work " is an essential ingredient of real life; but we feel that patients as deteriorated as ours are not ready for this. To compensate we encourage parole, leave, and the fullest possible enjoyment of hospital amenities outside the ward. Selected patients also go regularly to the factories with which we deal, and are brought, under protected conditions, into contact with the outside world.

We are indebted to Dr. George Somerville, physician-superintendent, for help, guidance, and encouragement. Mr. E. J. Latchford, chief male nurse, has given us continuity of staff and enthusiastic support. Miss M. D. Beldam, head occupational therapist, has placed her technical knowledge at our disposal and helped with her advice. Mr. E. V. Roxburgh, superintendent engineer, has met our persistent requests for apparatus. Mr. A. L. Lovell, the transport officer, has supplied us generously with his vans and lorries, so that we have not had to refuse any contract for lack of transport. To these and many others we gratefully acknowledge our debt.

CONVALESCENT TREATMENT

IN 1956 the Minister of Health appointed a working party, under the chairmanship of Dr. N. M. Goodman, to examine how far convalescent homes in the National Health Service are meeting the demands placed on them in the light of advances in medicine and modern conceptions of treatment and nursing care. Though their investigations were limited to four Metropolitan regional hospital boards their report [1] is of more than local significance, and their main recommendations are discussed in an editorial on an earlier page.

These include proposals for regrading convalescent facilities into homes where active treatment is given (to be known as convalescent hospitals), which should be upgraded where necessary, and homes for recuperative holiday type of care which should no longer be the responsibility of the hospital service; increased accommodation for specially difficult groups; a convalescent information bureau to coordinate the exchange of information and advice on placing. They also propose experiments with accommodation in or near hospitals, with facilities such as physiotherapy provided by the parent hospital, day convalescent centres based on the department of physical medicine at general hospitals in large centres of population, and the use of convalescent accommodation for patients who need preventive treatment and preparatory care before active therapy is begun.

As a background to their main recommendations the working party discuss practical problems which they met in their survey and they also offer suggestions on these important points of small and large details.

1. Convalescent Treatment. H.M. Stationery Office, 1959, Pp. 48. 3s.

Arrangements for the payments for convalescence contain many anomalies and to the patient at least often seem chaotic. The working party would like to see the system rationalised and the hospital service providing for all patients who need convalescent treatment, if necessary by altering or extending contractual arrangements.

For many patients the first difficulty of convalescence is getting to and from the home and paying for their transport. Often they are faced with a long tiring railway journey without adequate reservations. The working party recommend that the hospital service should pay railway fares or provide transport on medical certification.

Once the patient is in the home the main difficulties seem to turn on lack of medical liaison. The doctor at the home is sometimes reluctant to take full responsibility, yet the hospital consultant is usually too distant to supervise an ordered sequence of treatment. Local consultant treatment is seldom thought to be necessary by the doctors at the homes, and the cooperation of physiotherapy or occupational therapy departments is seldom sought. This divided responsibility means that the length of the period of convalescence is not reviewed when an extension is medically desirable.

In the running of the homes themselves one of the chief problems, as so often elsewhere, is shortage of staff. The need for more trained nurses is particularly acute and is often the reason for the refusal to accept difficult cases and apparently unreasonable restrictions, such as lack of rest periods, too early getting-up, and the impossibility of breakfast in bed. One of the chief causes of the shortage of staff is a sense of isolation and detachment from other forms of nursing. The post of matron is often held by an older woman nearing retirement, and the working party feel the appointment of younger keen, and active nurses and closer medical supervision to be essential for a more active policy on convalescence.

DOCTORS IN PARLIAMENT

IN last week's General Election ten doctors were elected to Parliament. One of them is a newcomer to the House of Commons—Dr. A. J. Glyn, Conservative member for the Clapham division of Wandsworth.

R. F. B. BENNETT, V.R.D., M.A., B.M. Oxon., D.P.M. (C., Gosport and Fareham), was first elected in 1950.

A. D. D. BROUGHTON, M.A., M.B. Cantab., D.P.H., D.P.M. (Lab., Batley and Morley), entered Parliament in 1949 by winning a by-election.

J. D. CRONIN, M.B. Lond., F.R.C.S. (Lab., Loughborough), first entered Parliament in 1955.

A. J. GLYN, B.A. Cantab., L.M.S.S.A. (C., Wandsworth, Clapham), graduated B.A. with honours at Cambridge in 1939 and after the war qualified from St. George's Hospital in 1948. He is in practice in Belgravia. He is also a member of the Middle Temple.

CHARLES HILL, P.C., M.A., M.D. Cantab., LL.D., D.P.H. (L. and C., Luton), was secretary of the British Medical Association from 1944 until he entered Parliament in 1950. He has held office as parliamentary secretary, Ministry of Food, Postmaster-General, and Chancellor of the Duchy of Lancaster.

D. McI. JOHNSON, M.A., M.B. Cantab. (C., Carlisle), qualified from St. Bartholomew's Hospital in 1926. He is also a barrister-at-law.

J. D. MABON, M.B. Glasg. (Lab. and Coop., Greenock), was elected to his present seat at a by-election in 1955.

Sir MALCOLM STODDART-SCOTT, O.B.E., M.D. Leeds (C., Ripon), was Conservative member for Pudsey and Otley from 1945 to 1950, since when he has represented Ripon. He was knighted in 1957.

BARNET STROSS, M.B., M.SC. Leeds (Lab., Stoke-on-Trent Central), has been in Parliament since 1945.

EDITH SUMMERSKILL, P.C., M.R.C.S. (Lab., Warrington), represented Fulham West from 1938 until 1955. Since then she has represented Warrington.

Conferences

PROBLEMS ARISING FROM CONTROL OF PESTS AND DISEASES

FROM A CORRESPONDENT

IN bringing modern technology to bear on the elimination of pests and diseases, biologists and doctors often become immersed in details. Thus, a campaign against malaria may critically depend on the behaviour of crystals of insecticide on dry mud walls of primitive dwellings; or a possible new method of eliminating sleeping-sickness may lead to investigations of the sterilising effect of gamma-radiation on male tsetse flies. Such questions occupy so much of the scientist's attention that he tends to lose sight of the main objective. Therefore, it was refreshing to take a wide view of the results of various biological and medical activities in a Symposium on Biological Problems Arising from the Control of Pests and Diseases, held in London on Oct. 1 and 2 by the Institute of Biology. Clearly some of these problems, such as accelerated population growth following reduction of disease in under-developed countries, will be very difficult to solve. But most speakers were convinced that these problems were at least less serious than the evils overcome.

Bacterial Resistance

At the final session Dr. MARY BARBER described the disturbing increase in strains of drug-resistant bacteria associated with the widespread use of antibiotics. Resistance seems to develop largely by selection of mutant types. There are two main resistant types: drug-tolerant and drug-destroying. The former become immune to the drugs, sometimes to the extent of being actually dependent on them. The drug-destroying strains survive because they produce enzymes, such as penicillinase, which destroy the antibiotic. Since the individual bacteria remain sensitive, resistance depends on the numbers of organisms present to produce the enzyme. This is the usual type of penicillin resistance in staphylococcal infections which involve very large numbers. Associated with the acquisition of resistance, there may be changes in viability, virulence, or even colour or form. Generally, the biological efficiency of the resistant strain is somewhat diminished. Possibly this accounts for the gradual decline in prevalence of resistant strains when the use of an antibiotic is abandoned.

Resistant strains of bacteria occasionally show cross-resistance to other drugs—particularly related compounds. On the whole, however, double chemotherapy with antibiotics of two types is a good way of preventing the development of resistance to either. Another precaution is the limitation of the use of antibiotics (especially those affecting many types of bacteria) to serious cases and to infections likely to respond. The general adoption of these policies has considerably improved the situation.

Resistance in Insects

The next speaker, Dr. JAMES BUSVINE, dealt with resistance to poisons by insects—in which there are interesting parallels and a few contrasts to bacterial resistance. Thus, while resistance to hydrogen cyanide was observed in citrus scale insects forty years ago, the enormous increase in resistant insects has been associated with the use of powerful new synthetic insecticides in the past fifteen years. In contrast to the bacterial situation, however, resistance seems to be possible in nearly every kind of insect. Reports of trouble have come from all over the world, involving over 100 species of pest. About half these insects are of public-health importance, and the most serious aspect is the threat to plans for eradicating such diseases as malaria, typhus, and plague—plans that depend entirely on the cheapness, effectiveness, and simplicity of the new insecticides.

Resistance in insects is definitely not a direct response to sub-lethal doses of poison: it is a pre-existing hereditable character which comes into prominence when widely used insecticides destroy preferentially the normal types. The inheritance of the character has been shown to be mendelian, often of a single gene allelomorphic to the "wild type". The genes for resistance are not necessarily linked to deleterious factors (unconnected with insecticides) so that resistant races, once selected, tend to persist for a considerable time after selection pressure ceases through discontinued use of a particular insecticide.

Resistant races are of two main forms: a "physiological" form, which becomes immune to the poison; and a "behaviouristic" form, which manages to avoid it. The former is by far the commoner. The important instances of physiological resistance are specific to certain classes of poison and confer more or less immunity to other poisons of the same type. The most effective of the numerous new synthetic compounds all fall into one of only two or three groups so that there are not many alternatives when resistance renders one type useless. It has been suggested that resistance could be delayed or prevented by using mixtures of two different types of insecticide (on the lines of double chemotherapy for bacteria); but the evidence available, which is admittedly mainly from laboratory experiments, is not encouraging. Houseflies selected by two types of insecticide develop simultaneous resistance to both groups.

The full weight of insecticide resistance has not yet been felt because of the alternative insecticides which are still effective. But the situation will be grave if resistance develops to all three classes of insecticide in the major pests. The numbers of instances are constantly growing, and every case is a defeat in the sense that a group of insecticides becomes ineffective for a certain pest for an indefinite period.

"Ethical" Selection

Dr. G. C. L. BERTRAM, speaking on Ethical Selection—the Supplanter of Natural Selection in Mankind, said that, after eons of Natural Selection, which is pitiless in eliminating the weakly, the diseased, and the stupid, human compassion had appeared, and given rise to charitable attempts to succour the infirm. But there was scarcely any appreciable effect on survival and reproduction until the great medical and scientific advances of the past hundred years. In the present century, in civilised countries, people with physical or mental defects have been carefully nursed and allowed to reproduce whether their disabilities are hereditable or not. Technological advances are now extending this compassionate care to under-developed countries. At the same time, advancing standards of living in urbanised countries have produced more complex human desires and behaviour, which have led to a spontaneous decline in the birth-rate. There is some reason to hope that the same voluntary limitation of population will extend to more primitive countries and thus prevent further serious overcrowding.

It seems likely that human actions which deliberately reduce natural births and deaths must eventually affect the evolution of our species. (Only the saving of lives in the reproductive span would be relevant in this respect, of course.) Dr. Bertram declared that we are assuming a serious responsibility in replacing natural selection by what he calls "ethical" selection.

This phrase evoked some criticism though no-one challenged his general thesis. Dr. Bertram explained that here "ethical" had no special moral connotation: it merely implied the operation of deliberate choice. Dr. BUSVINE suggested that the combined effects might be deleterious, since death prevention might preserve harmful genes and birth control was known to operate at present largely in the more intelligent section of the population. Dr. BERTRAM replied that there was so far no evidence of this. It was also remarked that birth control readily spreads throughout the whole community when a certain level of subsistence is reached; and, beyond a certain level, there is evidence of larger families (e.g., in the U.S.A.).

The symposium left the impression that, as regards the major problems resulting from control of pests and diseases, little can be done at present; but that it was well worth ventilating the facts.

NON-GONOCOCCAL URETHRITIS AND HUMAN TRICHOMONIASIS

FROM A CORRESPONDENT

THE first Canadian Symposium on Non-gonococcal Urethritis and Human Trichomoniasis was held in Montreal on Sept. 20–22, under the Chairmanship of Dr. PAUL BOURGEOIS, director-general of Notre Dame Hospital. About 150 doctors from 13 countries attended. The initiative in holding symposia on these conditions comes predominantly from the French-speaking peoples. Previous meetings were held at Rheims in 1957 under the auspices of the French Society of Gynæcology, and a symposium on non-gonococcal urethritis was organised at Monaco in 1954 by the International Union against the Venereal Diseases and Treponematoses.

In an introductory review of present knowledge, the ætiology of non-gonococcal urethritis was discussed by Mr. A. J. KING (London), treatment by Dr. P. DUREL (Paris), and trichomoniasis in the female by Prof. GASTON CHAPPAZ (Rheims).

Non-gonococcal Urethritis

There were a number of possible causes (virus, pleuropneumonia-like organisms, bacteria, fungi, and trichomonal infestations), and the small proportion of cases in which probable viral inclusions has been found were discussed by Prof. G. MOUSTARDIER (Bordeaux). Pleuropneumonia-like organisms (P.P.L.O.), while favoured by some (Dr. A. GRIMBLE [London] found them in 184 out of 608 patients with non-gonococcal urethritis), were thought to be commensals by others, and Dr. T. NASEMANN (Munich) had found them in healthy adults and children. Dr. M. C. SHEPARD (Camp Lejeune, U.S.A.) favoured the so-called T strains which were difficult to culture. Such strains were often not picked up by the usual cultural techniques and he considered that many so-called "virus bodies" seen by other workers were in fact P.P.L.O. The relationship of P.P.L.O. with L forms of other bacteria was undecided.

No new evidence was produced to incriminate *Hæmophilus vaginalis*, although Prof. P. POPCHRISTOV (Sofia) thought that many cases of non-gonococcal urethritis were due to invasion by bacteria when the normal bacterial flora of the urethra (which were said to produce antibiotic substances which protected against infection) had been inhibited by antibiotics given to the patient.

Trichomonas vaginalis was responsible for a definite but as yet undetermined proportion of cases of non-gonococcal urethritis. Dr. EDNA INZUNZA (Santiago, Chile) believed trichomoniasis to be a generalised disease and capable of producing sterility in the male (by causing epididymitis or occlusion of the ejaculatory ducts) and ejaculatio præcox.

Treatment

Little new was offered in the treatment of non-gonococcal urethritis. Broad-spectrum antibiotics gave the best results although the justification for their mass use in the first instance was questioned on grounds of expense. Dr. J. ETHIER (Montreal) claimed only 16% of failures (when trichomonas-positive failures had been eliminated) with spiramycin. Dr. R. R. WILLCOX (London) said that the addition of methylprednisolone had no effect on the failure-rate in non-gonococcal urethritis treated with tetracycline.

The use of a new amidazole derivative, hydroxy-2-ethyl-1-methyl-5-nitroamidazole (allied to the Japanese product azomycin), was described by Dr. P. DUREL (Paris). Relatively non-toxic (although theoretically capable of hæmopoietic side-effects) it was lethal to trichomonads in vitro, and prevented trichomonal abscesses in mice. 250 mg. twice daily for 10 days had had no effect on 14 cases of non-gonococcal urethritis in which trichomonads had not been found, but in 13 trichomonas-positive cases the parasite disappeared in all, although the urethral discharge remained in 2. There had been slight gastric troubles in some cases with diarrhœa, and headache and flushing in 1 case. Better results were claimed than with any other previous product systemically administered.

The treatment of trichomonas urethritis in the male has been unsatisfactory. Local treatments have given the best results. Dr. R. D. CATTERALL (Leeds) had 60–74% of cures with irrigations of potassium permanganate, oxycyanide of mercury, or dequalinium chloride. Dr. B. H. KEAN (New York) had good results with carbarsone by mouth in doses of 250 mg. three times a day for 10 days, in conjunction with local treatment in both sexes. He claimed 17 of 22 couples cured, although 5 required two courses of therapy.

Trichomoniasis

Dr. KEAN said that cultures of trichomonads urethritis may not become positive before the 5th to 7th day of the disease. Prof. G. CHAPPAZ (Bordeaux) considered *T. vaginalis* infections to be practically always sexually acquired, as did Dr. CATTERALL, who found the parasite in 85% of the female contacts of 67 males with trichomonatous urethritis. He admitted, however, the possibility of non-sexual transmission—e.g., by lavatory seat.

Dr. F. B. CARTER (Durham, North Carolina) claimed "control" in 104 out of 112 cases by local lactic acid. It was contraindicated in diabetes and in the presence of mycoses. The treatment did not prevent relapse, however.

The method of Dr. L. G. FEO (Philadelphia) was to correct other local lesions, immediately after the menses, by cervical cauterisation and calibration of the urethra where necessary, and to give a broad-spectrum antibiotic for 7 days. Then, after the next two periods, the vagina was washed in oxycyanide of mercury, dried, and an aqueous solution of merthiolate (1 : 1000) instilled into the urethra and cervix. The vagina was then insufflated with a medicated powder daily for 3 days, on alternate days for 6 days, and the procedure was repeated immediately after the next period. Œstrogens were then given for 3 weeks to coincide with the normal menstrual rhythm, and abstinence from coitus was insisted upon for 3 weeks. If recurrence followed, the male consort was examined to distinguish between relapse and reinfection. Dr. Feo indicated that *T. vaginalis* was a harmless saprophyte in some cases and no treatment was necessary.

There was a need for an effective substance which could be given orally to prevent auto-reinfection of the female from unkilled trichomonads in Skene's tubules and other sites and from reinfection by the male. Dr. Feo indicated from experiments with sulphonamides that only small quantities of systemic drugs appeared in the vagina, compared with the blood and urine. In an acute infection, or during a menstrual period, larger quantities might appear in the vagina from the blood. Dr. WILLCOX described the almost total failure of aminitrozole and the Japanese antibiotic, trichomycin, to cure vaginal trichomoniasis when given systemically without other measures.

Dr. LISE FORTIER (Montreal) treated 31 cases with amidazole giving 250 mg. twice daily for 10 days by mouth plus 500 mg. per vagina. There were 3 failures; and 2 failures out of 8 patients treated by the vaginal route only. Dr. DUREL said that 1 case in 4 failed if only the vaginal route was used (mixed treatment was required for the drug to get into the urine) and he had had 4 failures out of 21 cases on combined therapy. Oral therapy alone was used in 6 cases, with 1 failure.

The economic waste due to *T. vaginalis* was appalling, declared Dr. D. C. MCEWEN (Regina): the world was filled with miserable women. He regarded emotional tension as a factor in 70% of cases, in which failure to treat the tension sometimes led to failure. Emotional stress, he felt, would alter the metabolism of the vaginal cells and encourage infestation with *T. vaginalis*. Not all agreed with him, and some felt that the emotional tension was the result, not the cause, of the condition.

The symposium emphasised that more money was required for research into trichomoniasis. The venereologist was the best man to treat it, for he is better equipped than the gynæcologist or urologist to deal with disease in both sexes.

HEPATITIS

FROM A CORRESPONDENT

AT the meeting of the Czechoslovak Society of Gastroenterology and Nutrition in Carlsbad on Sept. 20–24 one of the main themes was hepatitis.

Dr. V. KUBELKA (Prague) has isolated a virus (the Motol virus) from the blood of patients with infective hepatitis. After one passage on the chorioallantoic membrane of nine-day-old chick embryos, it showed specific cytopathogenic effects in the course of 35 passages in monkey-kidney-tissue cultures, although it failed to reveal such effects in Hela-cell culture. It caused fatal hepatitis in mice, and also agglutinated various animal erythrocytes in the cold. Intradermal injections of the inactivated formolised virus produced an allergic reaction in 60% of patients convalescing from hepatitis, compared with 15% of control subjects.

Dr. A. K. SHUBLADZE (Moscow) has also isolated a virus from the blood of patients with hepatitis, and maintained it in chick-embryo fibroblast tissue-culture. Another strain from dog hepatitis has been grown in dog-kidney tissue-culture. Neither strain could be adapted to Hela cells. She noted certain similarities between the human and dog strains: both were associated with intranuclear elements in liver cells, and both had hepatoencephalotropic properties. The severity of canine hepatitis was much more pronounced if there is accompanying spontaneous infection with *Pasteurella pestis* or a non-hæmolytic streptococcus. Synergistic bacterial and virus infection resulted in a mortality of almost 100%, compared with 10–20% among dogs affected only by virus hepatitis. Dr. Shubladze had not established the specificity of these various human and animal hepatitis viruses by serological means. They were antigenically related to viruses of the spring-summer and Japanese encephalitis group, but not to other neurotropic viruses such as Coxsackie, herpes, lymphocytic choriomeningitis, rabies, and equine encephalomyelitis.

Since 1950, notification of infective hepatitis has been compulsory in Czechoslovakia, and this has aided epidemiological studies. Dr. K. RASKA (Prague) said that epidemics started in schools, and it was three times commoner in children attending nursery-schools. These school endemics had smouldered on for six to ten months, until prophylactic γ-globulin had been introduced.

Dr. J. HONEJSI (Prague) suggested that the most satisfactory biochemical tests were the enzymatic ones, such as the level of serum-transaminase activity. Although more sensitive than the commonly used flocculation tests, none provided a specific diagnosis, which depended on virus isolation and the development of standard serological and skin tests.

Dr. I. B. BRICK (Washington) drew attention to extrahepatic manifestations which were sometimes overlooked, but often provided valuable pointers to the diagnosis of chronic hepatitis or cirrhosis. They included white, ridged, and clubbed nails, muscle wasting, red palms, xanthomas and pigmented creases, parotid enlargement, Dupuytren's contractures, and vascular spiders.

Dr. J. CAROLI (Paris) presented a strong case for combining diagnostic aspiration biopsy of the liver with direct inspection of the liver by laparoscopy and even laparophotography. Colour photographs obtained by peritoneal endoscopy aided anatomical classification, helped in assessing the prognosis, and, when recorded serially, were useful in evaluating the response to treatment.

Dr. E. KLIMKOVA (Prague) drew attention to the value of electroencephalography in evaluating the neuropsychiatric sequelæ. Although not specific, the slow waves might be helpful in following the course and assessing the response to therapy. Dr. J. LIBANSKY (Prague) had analysed a series of twelve cases in which prolonged hyperbilirubinæmia had followed acute hepatitis. This condition must be distinguished from Gilbert's familial jaundice and from congenital hæmolytic states.

In England Now

A Running Commentary by Peripatetic Correspondents

William Harvey, when he left England in 1636 accompanying the Earl of Arundel on his embassy to the Emperor of Germany, took great pains that his *sede* was in order and we can imagine his chagrin when, to use his own words, he received "a very unjust affront being stayed and commanded by this podesta to have gone in the lazeretto with no cause or suspicion alleged". He chose the open fields rather than the lazeretto and there he was detained, although he said "my business requires expedition" for "God knows how long". A letter to the Ambassador, Lord Feilding, produced some amelioration of his living conditions, but he suffered an attack of sciatica and when he had been impeded in his progress for eleven days a heavy message from the Senate of Venice said he must wait another seven or ten or twenty days.

I, like Harvey, set out this year thinking all was in order, but I was wrong. I wanted to cross the Transjordan/Syrian border en route for Lebanon. Transjordan and Syria have broken off diplomatic relations. The protecting power, Indonesia, issued a visa for transit but presentation of it at the frontier got the simple remark, "You have been in Israel and it is illegal to enter Syria". I had to retreat to Jerusalem, fly to Beirut, which cost an extra £10, and saw Damascus only from the air. Later when I was on the boat from Cyprus to Turkey, a fellow passenger who heard I was taking the Orient Express home, asked if I had any difficulties getting visas for Bulgaria and Jugoslavia. My agent in England told me this was unnecessary if I didn't get off the train. How wrong he was. Remembering the golden rule of travellers—"There is always the British Consul"—I consulted him on arrival at Izmir (the modern corruption of Smyrna), and he verified that I must have visas which I could get at Istanbul. There the British Consul said I would be lucky if I got them in 48 or 72 hours, and that the Bulgars were very difficult. In Izmir I got my photographs in two hours. On arrival at Istanbul I got some extra Turkish money and was at the Jugoslav Embassy at 10.30 A.M. and received my visa by 11.15 A.M. and was at the Bulgarian Embassy at 11.30 A.M. and was told, after filling up a form, to call for the visa next day. Explaining that I must travel that afternoon to attend a medical conference in Germany, I was sent to a higher authority who said he would do it if he had time and if I would wait. His interpreter said, "The Consul is very kind, he will help you". By 12.20 P.M. I had the visa, took a taxi to the Golden Horn, had lunch with a friend, visited St. Sophia's (its mosaics being beautifully uncovered from Moslem plaster by Oxford and Harvard graduates), the Blue Mosque, and the erstwhile Sublime Court, and got the Orient Express at 15.45, feeling my curses which I thought I would cast on the Bulgars should be reserved for the English agent who had wasted the only morning I had to spend in Istanbul.

However, I felt my fate was evidently better and less deserving than Harvey's.

* * *

Time marches on and the sea is almost empty. The last ice-cream van has disappeared, and the last fish hook has been drawn from swollen finger and reluctant fish. But let's admit it, we still have our fun. What with carnival procession, circus, and election all squeezed into two glorious days we hardly knew where we were. The carnival was the best ever; the circus, for once in the centre of the town, took care of the crowd when the procession had passed. After that of course there was no time to go to the last-night electioneering speeches. We didn't worry. We all knew whom we were voting for, so why risk getting muddled at the eleventh hour? Thursday came, and what with T.V., wireless, and loudspeakers going round the town it was every bit as good as last night's circus and nothing to pay. Friday the whole town slept late. After all we had done our bit. We had voted and stayed up till 4 A.M. watching it all on T.V. and had earned our rest. Then Sunday and the anticlimax. The moon has lost its moon face. Truly

the Russian splodge of blue paint must have knocked it sideways, or had Eisenhower's voice at Christmas shaken it out of shape? It doesn't matter. We have had our two days of excitement, and now we can take the moon and its moon face in our stride.

* * *

The question of a unified medical service for the Armed Forces has been raised again, partly, I imagine, in the hope of lessening the internecine strife that enlivened the quieter periods of the late war. We temporary gentlemen were mere pawns in this game. One evening in a Middle East mess the P.M.O. told me over a drink to go next day to an Army psychiatric unit some 60 miles away to look at three patients whom it was proposed to fly home. Casually he pointed out that we had no aircraft in which the passengers were separated from the pilot.

In the morning I set off in the P.M.O.'s car. I had difficulty in persuading the driver not to fly the flag to which I was apparently entitled, because he took pleasure in watching the lesser fry salute it, but since he ended the journey by colliding with a native bus, I felt I had been right. The psychiatric hospital gave me an excellent lunch, and at length the patients were brought out. The first was a six-foot giant who dominated the proceedings from the start. "Ah," he said on seeing me, "a wing-commander of the Royal Air Force!" "Yes," I said. "You fly?" "Yes." "Where (in a tone of menace) are your wings?" "Well—er you see, I'm a medical officer." "Ah, you fly with God." At this point he was persuaded away. The next was equally wild, but mute, and bandages round neck and wrists testified to a recent attempt at suicide. The third was a small harmless dement of the type usually seen cleaning the medical superintendent's car outside mental hospitals. "We might fly the third," I said, "but I doubt if anyone would take off with the other two." "A pity," said the psychiatrist, "I had hoped to send the first two under care of the third."

The matter seemed simple to me, and I went back and made my report. Shortly afterwards I was demobilised. Perhaps I should have noticed the glint in the P.M.O.'s eye, and realised that the lunch was too good. For my excursion, I was later told, was the opening shot in a battle which echoed far beyond the desert sands, through H.Q.s and places where they write minutes, to the very doors of Whitehall itself. Charges of wilful lack of cooperation went to and fro, and it was long before the thunder died away.

The point is this, would peace have come sooner if we had had one Director General, one H.Q., instead of three? Personally, I doubt it.

* * *

She was a sophisticated young woman of the modern school. I am bound to admit that we were rather surprised at her first antenatal attendance to note that her religion had been recorded as "Nun". Closer questioning clarified the matter and we altered the entry to "Atheist".

* * *

HERE COMES THE YOGA MAN

Simple, simple little dimple
Full of mystery and awe—
On the level, little navel,
What the devil are you for?

The spell, I fear, might disappear
If you should ever drop your mask
But none the less I must confess
I seek an answer when I ask.

Never was a deeper fossa
Never secret kept more close;
You've forgotten, subtle button,
More than any of us knows.

Willow, wallow, little hollow,
Holding the gorgeous East in fee;
Tell my fortune, I importune—
What is there in you for me?

Letters to the Editor

TALKING SENSE

SIR,—Thank you for publishing Dr. Asher's lectures (Sept. 19 and 26), which I enjoyed. Much of medicine is a semantic maze strewn with verbal banana skins. This is partly because doctors are too busy to read, think, and reflect enough. There are too many patients and too many papers. Additionally, we are undereducated in the art of critical reasoning. It is high time to develop the field I call Clinical Logic. The approaches could be observational, experimental, analytic, and methodological. For example, given leisure and a tape recorder we could "take apart" our procedures in history-taking to elucidate and develop the better techniques. Again, by thinking aloud on to tape we could try to record our thoughts on differential diagnosis of a case. The premises and reasoning could then be assessed and analysed. Such investigations, as well as being entertaining, might produce results of formal and practical value.

I am disappointed that Dr. Asher has doubts about the value of teaching logic to students. Certainly the old elementary propositions are not the types of reasoning used in medicine. However, I believe that the "new" symbolic logic has even now important applications to medicine. The logical processes used in diagnostic reasoning can be formulated in terms of problems involving overlapping classes.[1] The form of argument suitable for use in diagnostics is a massive expression to wield thus:

If manifestation (e.g., a symptom or sign) alpha has been described in diseases a, d, e, f, &c., to, e.g., 50 items; and
If manifestation beta has been described in diseases b, e, g, n, &c., to, e.g., 100 items; and
If manifestation theta has been described in diseases c, e, j, z, &c., to, e.g., 70 items; then
Manifestations alpha, beta and theta have been described in disease e, &c.

This activity may be termed the conjugation of manifestations.

In addition to the books mentioned by Dr. Asher, the following may assist in the development of clarity of thought and expression:

Origins (Partridge)
The Reader Over Your Shoulder (Graves and Hodges)
Logic for Everyman (Mander)
Language in Thought and Action (Hayakawa)
The Tyranny of Words (Chase)
A Modern Introduction to Logic (Stebbing)
Introduction to Logic and to the Methodology of Deductive Sciences (Tarski).

If a Section of Medical Logic were formed in the Royal Society of Medicine I wonder how many would be interested?

Western Hospital,
London, S.W.6. F. A. NASH.

THE NATURE OF EXPERIENCE

SIR,—I was most intrigued by the animadversions of Mr. Jelly and Dr. Heaton (Sept. 26) on the subject of the sense datum theory. Their objections to the theory appear to spring from two quite diverse causes, for whilst Mr. Jelly displays a certain scholarly inflexibility in his discourse on abstract art, Dr. Heaton's argument is characterised in the main by a belief in his own Socratic method which is scarcely justified by his subsequent "logical" analysis of his point.

1. Nash, F. A. *Lancet*, 1954, i, 874.

It was rather difficult to decide from their written opinions whether they were dissatisfied with the sense datum theory as such, with Sir Russell Brain's advocacy of it, or with the account (Aug. 29) of Sir Russell Brain's exposition, but since for the purpose of discussion one has to assume that they have actually read all three and not merely the review, one must consider their remarks in the absolute, as an attack on both the theory and its neurological support as expressed by Sir Russell and in the article.

Dr. Heaton, it seems, believes that " the sense datum theory collapses because it takes no account of the series of events which makes the perceiver attend to a perception ". This is a monumental non sequitur. Whatever views one may have upon present living and future immortality, one can see nothing in perception which is not explicable by cortical physical events. Of course the perceiver can perceive himself perceiving, but that in no way makes him a series of events in his own cortex as Dr. Heaton suggests, though it does allow him to be appreciated there (him and his actions) as the result of physicochemical activity. Disturbances of the *image de soi* which occur in structural lesions of the parietal lobe indicate the importance of cortical physicochemical integrity in this phenomenon of self-perception. As to Dr. Heaton's concluding remarks, our ability or otherwise to say whether or not another person is having perceptions is totally irrelevant to the discussion.

Mr. Jelly's analysis of the origins of abstract art is indeed admirable. One presumes that he accepts the value of the sense datum theory in the explanation of the complex relationship existing between object, artist, and observer in representational art. The point raised by the theory's application to abstract art (inadmissible to Mr. Jelly) is that there must still be a relationship between observer and artist dependent upon differential sense data in the two brains but functionally linked by an object for which the source must be a series of physicochemical events in the brain (mind) of the artist. An external concrete object is quite unnecessary to evoke this chain of events and a near-blind artist (though not one totally so) is indeed quite permissible, as Mr. Jelly says.

Mr. Jelly appears to regard physicochemistry (his own noun, by the way) as a kind of surrealist ectoplasm with specific active and passive qualities, but this is to deny the essential dynamism of neural function. In any event, despite Mr. Jelly's sources of origin of abstract art, there seems to be a genuine point of application of the sense datum theory to this artist-observer relationship.

The Royal Infirmary, Manchester. L. A. LIVERSEDGE.

OSTEOCHONDRODYSTROPHY OR DYSPLASIA EPIPHYSEALIS MULTIPLEX?

SIR,—Dr. Lomas and Dr. Boyle (Sept. 26) are to be congratulated on reporting on 75 out of 79 members of a family through three generations and finding 31 cases of osteochondrodystrophy (Morquio-Brailsford).

The range of skeletal disturbance varies from the minor involvement of metacarpals (cases 8, 9, 10) to severe involvement of the spine, pelvis, and hands.

Osteochondrodystrophy may be a satisfactory term for severe affections resulting in the characteristic clinical picture of dwarfism, thoracic kyphosis, waddling gait, and stubby hands. It is extravagant for the minor affections involving only the hands. Indeed, Brailsford [1] himself reported a case of hand and hip involvement under the heading, Familial Brachydactyly with Associated Bilateral Coxitis, and not as a type of osteochondrodystrophy.

Fairbank [2] reported a series of cases which had irregular ossification in several epiphyses, and one at least had been previously reported as osteochondrodystrophy, using the descriptive term " dysplasia epiphysealis multiplex ". These cases did not appear to have spinal changes nor familial or hereditary influence, like the Morquio-Brailsford type, but recent papers [3–6] have reported both the hereditary influence and some spinal changes.

It seems probable that cases are classified under either osteochondrodystrophy or dysplasia epiphysealis multiplex with resulting confusion, and delay in the full understanding of the width and pattern of epiphyseal affections. Until such time as a name based on ætiology can be used for this group, one based on description must suffice. I would urge the use of dysplasia epiphysealis multiplex for these less severe affections and reserve the term osteochondrodystrophy for the severe clinical and radiological entity described by Morquio [7] and Brailsford. [8]

Heatherwood Orthopædic Hospital, Ascot. ROY H. MAUDSLEY.

THE ÆTIOLOGY OF LEUKÆMIAS

SIR,—I am glad Dr. Laws (Oct. 3) wrote on this subject as he did. The article by Dr. Schöyer (Sept. 19) added nothing to our knowledge of the leukæmias and could have been ignored had you not followed it with a leader to which you gave the title New Thoughts on Leukæmia. The truth is that we have spent too much time on vague generalisations about the cancer cell and the neoplastic process. We must, as Dr. Laws indicates, express ourselves in more precise biochemical terms that will explain on the one hand the clinical picture of the leukæmias and on the other the mass of information we now have of the biochemical differences between normal cells and those that are neoplastic. Those who doubt this should read the searching article by Jacob Furth [9] summarising his thirty years' study of the problem.

It will greatly assist if we cease talking about " the cause " or " the ætiology " of the leukæmias or other neoplasias and confine ourselves to " the mechanism ". It is clear that whatever the " cause " of neoplasia, treatment must ultimately depend upon a knowledge of how the process, once initiated, goes on.

If we discuss only leukæmia we now know that the trigger for this disease is very often radiation. Let us accept that for the moment and drop arguing about " cause ". There is enough evidence to indicate that the mechanism involves a change in the desoxyribonucleic acid of the cell nucleus: a change which leaves the cell capable of reproduction but removed from what Dr. Laws rightly calls " those cellular and tissue mechanisms which normally maintain a regular, numerical, spatial, contactual, and functional relationship between cells ". The degree of that change and the number of cells involved dictate the rate of development and the clinical manifestations of the disease.

The process, being a biological one, will certainly be complex and may indeed involve an alteration in substances which may merit the term " inhibitor " although that term is certainly foreign to the metabolism of the normal cell. We are surely dealing with a derangement of balanced forces, enzymatic and possibly metallic, and the new thought that will find the cure for leukæmia must clarify the biochemical derangement in precise terms.

Kingston Hospital Surrey. D. STARK MURRAY.

1. Brailsford, J. F. *Brit. J. Radiol.* 1946, **19**, 127.
2. Fairbank, H. A. T. *Proc. R. Soc. Med.* 1946, **39**, 315.
3. Waugh, W. *J. Bone Jt Surg.* 1952, **34B**, 82.
4. Maudsley, R. H. *ibid.* 1955, **37B**, 228.
5. Shephard, E. *ibid.* 1956, **38B**, 458.
6. Barrie, H., Carter, C., Sutcliffe, J. *Brit. med. J.* 1958, ii, 133.
7. Morquio, L. *Arch. Med. infant.* 1929, **32**, 129.
8. Brailsford, J. F. *Amer. J. Surg.* 1929, **7**, 404.
9. *Cancer Res.* 1959, **19**, 241.

LOCAL COMPLICATIONS OF INTRAVENOUS THERAPY

SIR,—The paper by Mr. McNair and Mr. Dudley (Sept. 19) makes grim reading, particularly in connection with gangrene following intravenous infusion. It is indeed fortunate that this is a rare complication. I note that all the cases they describe are of the lower limb and that they tend to incriminate the long saphenous vein as being particularly vulnerable in this respect. I am sure that the poor state of the peripheral circulation is the major factor, and I remember most vividly a poor girl of 18 who developed a gangrenous right hand following transfusion into a vein on the dorsal aspect of the wrist.[1]

It is easy to understand why there are more cases of lower-limb gangrene. Despite condemnation of use of the long saphenous vein at the ankle for infusions, there is no doubt it remains the most commonly used site. Its position is so constant and easy to find, especially in the collapsed patient and in a child. The tragic case of this young girl, however, illustrates that the same disaster can occur in the upper limb with the use of a vein at a site which is now the main field for anæsthetists.

If this complication is actually due to a "reflex" mechanism[2] and is in any way related to the amount of muscle in the vein as the source of afferent impulses, there is much to be said for insisting upon use of veins at the root of the limbs, whether upper or lower, for transfusing cases of severe shock. This important point should be stressed to young doctors, into whose hands this task almost invariably falls, and borne in mind by the seniors who order it. It would probably be safer in these desperate cases to forsake the veins entirely and perform arterial transfusion at the outset. Here also, the larger the vessel, the safer the procedure.

This involves a certain amount of anticipation on behalf of the members of a surgical team, and although this unit has a sterile arterial transfusion set always available, I do not think there are nearly enough of these ready for use up and down the country.

Stobhill General Hospital, Glasgow. F. T. CROSSLING.

SIR,—I should like to comment on certain points in the article by Mr. McNair and Mr. Dudley.

They concluded that heparin is without effect in preventing thrombophlebitis. It is more correct to relate this failure to this particular thrombophlebitis-producing technique. Nobody doubts the anticoagulant action of heparin which is quite effective when used with other types of infusions.

They condemn heparin: "not only is it ineffective but serious accidental hæmorrhage resulted from erroneous administration of large doses". I am sure this is not the mistake of heparin. The dose recommended is a locally anticoagulant dose of 1 unit per ml. of infusion. This dose has no systemic effect even if used for long periods.

They advocate instead hydrocortisone. This should be accepted very cautiously. Considering the frequency of these infusions, a large number of patients will receive corticosteroids, and exposure of the patient to any stress later on may necessitate hormonal support.

Regarding caval catheters. I had the chance to perform ten catheterisations of the inferior vena cava at Preston Royal Infirmary. All the drips were heparinised. Two patients died (cause of death had no relation to the drip), and in both I found a thrombus extending from the site of the venepuncture at the long saphenous vein to the end of the polythene tube in the inferior vena cava. The process of thrombosis stops where local heparinisation is acting.

I think caval catheters should be used when there is absolute indication, infusions should always be heparinised, and it is better to call them iliac catheters and not to push them far in the vena cava.

Abbasseya Faculty of Medicine, Cairo. M. MAHRAN.

1. Vaughan, A. B. *Brit. med. J.* 1952, ii, 1097.
2. Dudley, H. A. F. *Edinb. med. J.* 1949, **56**, 557.

SIR,—May I dispel just a little "the unjustifiably gloomy picture of intravenous therapy" drawn by Mr. McNair and Mr. Dudley by quoting an unusually satisfactory intravenous drip.

In 1951 a six-year-old boy with generalised peritonitis and then a fæcal fistula was receiving intravenous therapy consisting of dextrose and saline in varying proportions. For a period of time chlortetracycline was added to the drip.

The apparatus consisted of the standard red-rubber drip set with a Hamilton Bailey cannula "cut-down" on the long saphenous vein at the ankle, the cannula being held by a chromic catgut ligature around the vein.

To our utter astonishment the drip ran uninterrupted and trouble-free for 21 days before the cannula fell out owing to the dissolution of the catgut.

I regret to report that this experience has not been repeated and that since then the normal incidence of thrombophlebitis has occurred.

London, W.1. B. ALTMAN.

THE ST. THOMAS'S OPERATION FOR ULCERATED LEGS

SIR,—I was very interested to read Dr. Rivlin's letter of Oct. 3 concerning this operation. In all fairness to the surgeons, it may be possible that Dr. Rivlin sees only their failures. The whole question would be readily resolved if surgeons Cockett and Linton were to give us their long-term results without compressive bandaging.

Dublin. J. BARNES.

RETINOPATHY FOLLOWING CHLOROQUINE THERAPY

SIR,—I read the article by Mr. Hobbs and his colleagues (Oct. 3) with great interest.

Among over 100 patients who have been under observation for several years and who have received chloroquine in large doses for longer than eighteen months, we have had 1 case with a serious complication affecting the eyes comparable to those described by the authors.

A woman of 34 was first seen in 1953 when she gave a few months' history of active rheumatoid arthritis which was in 1954 treated with bed rest, blood-transfusions, artificial fever, and small doses of gold. She made a good recovery but in 1956 she had a recurrence and she was then put on chloroquine sulphate 200 mg. t.d.s. (Nov. 17, 1956). Treatment proved very effective and she was practically symptom-free by May, 1957, when the chloroquine was cut down to two tablets daily. In November, 1957, when she was still symptom-free on 400 mg. chloroquine sulphate, bleaching of her hair was pronounced. In March, 1958, she was still quite well and mentioned no undesirable symptoms apart from "platinum blonde" hair. In April, 1959, she mentioned blurred vision and the appearance of haloes surrounding objects. Chloroquine was therefore stopped. In June, however, her eyes had not improved and she was unable to read and could not see anything clearly unless she looked towards the side of the object. Dr. Dorothy Barton confirmed bilateral pallor of discs and moderate attenuation of arteries (partial optic atrophy). There was bilateral clear-cut disciform degeneration of both macular areas. There was an absolute central scotomata in both eyes.

Inquiries at the time at the medical research department of the makers of chloroquine sulphate revealed no account of similar cases in the literature.

Having read the article in *The Lancet*, I have little doubt that the probably irreversible eye changes were the direct result of the antimalarial chloroquine over a period of two and a half years.

I entirely agree with Mr. Hobbs and his colleagues that chloroquine treatment of rheumatoid arthritis, lupus erythematosus, or other condition, should not be unduly

prolonged. I shall in future consider eighteen months' treatment the upper limit.

The benefit most patients with active rheumatoid arthritis receive from chloroquine [1] undoubtedly outweighs the side-effects which have been reported so far. Supervision of all patients on prolonged antimalarial treatment is, however, desirable.

Liverpool. H. FULD.

ABRAHAM FLEXNER

SIR,—Your informative obituary notice does perhaps tend to suggest that this great man had an exclusive predilection for professorial units in the process of medical education.

I am without prejudice in this direction; but I am reminded of an occasion when I had the privilege of a tête-à-tête conversation with Flexner some fifty years ago. He was then in London collecting evidence from various sources and I had had the honour of being presented to him (as a comparatively intelligent medical student).

Remembering many details of that interview, I was tremendously impressed by his insight. But, above all, I very clearly remember his saying to me: "First and foremost I want to create and establish in America a corps of general practitioners such as you have in this country."

The Chelsea Hospital for Women, London, S.W.3. FRANK COOK.

RISKS ASSOCIATED WITH MODIFIED ELECTROPLEXY

SIR,—The death associated with prolonged apnœa due to suxethonium bromide, described by Dr. Campbell (Sept. 19) and commented on by Dr. Davies (Oct. 3), is fortunately a rare kind of sequel of modified electroplexy. But the whole matter of how far the continued use of the modified technique is justified at all, surely arises.

It is a complicated and involved technique, for which it is usually held to be desirable that a professional anæsthetist should apply treatment jointly with a psychiatrist. The anæsthetist injects not only a muscular relaxant, but a barbiturate anæsthetic to relieve the patient of the horrible feeling of loss of muscle power. But electroplexy is itself a very effective anæsthetic. It seems a strange situation that two different types of anæsthetic must be given to safeguard the patient from clonic movements.

Compare modified electroplexy with "Ectonus", a technique which has now been available in this country for just over three years. Barker and Baker [2] felicitously described this method as "electrical modification of the convulsion". The ordinary method of applying ectonus involves elimination of all major clonic movements, giving a sustained tonic seizure. For patients with physical lesions, old fractures, or other conditions which make clonic movements undesirable, ectonus is safer than modified E.C.T. and is a more effective method of controlling clonicity. Ectonus [2–6] is the only form of electrotherapy which allows the therapist to be "on top of" the treatment situation all the time. With modified electroplexy once the injections have been given and the current passed, one has to accept what follows. Even in expert hands a good proportion of cases show more clonicity than is desired. With ectonus, during the seizure itself, any clonic movements which appear can be immediately eliminated by a slight increase in voltage.

Lennox Castle Hospital, near Glasgow. ALLAN A. MACDOUGALL.

1. Fuld, H., Horwich, L. *Brit. med. J.* 1958, ii, 1199.
2. Barker, J. C., Baker, A. A. *J. Ment. Sci.* 1959, **105**, 339.
3. MacDougall, A. A., Campbell, D. *Nursing Mirror*, Nov./Dec. 1957.
4. Russell, R. J., Page, L. G. M., Jillett, R. L. *Lancet*, 1953, ii, 1177.
5. Sargant, W. *Lancet*, 1958, ii, 1370.
6. MacDougall, A. A. *ibid.* p. 1180.
7. MacDougall, A. A. *Lancet*, 1959, i, 99.

ENDOGENOUS HYPOGLYCÆMIA

SIR,—In your annotation of Oct. 3 you mention the occurrence of endogenous hypoglycæmia in infants, and then discuss laparotomy and partial pancreatectomy. It was McQuarrie [1] who first showed that most of these children need never come to surgery.

When hypoglycæmia in infants is causing symptoms, and causes such as glycogen storage disease, galactosæmia, and pituitary, adrenal, and thyroid failure have been excluded, there are two simple tests which should precede surgery; and a positive result in either should preclude it.

One is the leucine (or casein) tolerance test.[2] If this reveals leucine sensitivity then extra carbohydrate at mealtimes should help, while there is no indication for pancreatectomy.

The other is a therapeutic test with corticotrophin (A.C.T.H.) (conveniently given intramuscularly as the gel). In the leucine-insensitive variety of idiopathic infantile hypoglycæmia this causes a sharp rise in blood-sugar [3] even to hyperglycæmic levels, which is found in none of the other conditions.[2 4–7] In severe cases the rise may last only a few hours, and the best time for blood-sugar estimations is between one and two hours after giving corticotrophin. A positive result thus allays fear of that rarest of causes of hypoglycæmia in infants, islet-cell tumour, and suggests the use for treatment of corticotrophin which gives excellent long-term results.[1]

When both tests are negative, surgery is a last, and unfortunately often unavailing, resort.

London, N.W.3. M. KINSBOURNE.

SIR,—Your otherwise comprehensive annotation on endogenous hypoglycæmia does not mention that most clinical studies have been based on inaccurate and, indeed, almost irrelevant estimates of "blood-sugar". Middleton [8] found that this might be anything from 0 to 81 mg. per 100 ml. higher than the blood-glucose and that this variation was irregular and unpredictable. It is not surprising, therefore, that there should often be no close relation between the blood-sugar level and the development of symptoms. When observing the effect of one variable upon another it is as well to be certain that the two relevant variables are actually being measured. It is to be hoped that the routine use of glucose-oxidase methods of estimation will provide a sounder scientific basis.

The Derbyshire Royal Infirmary, Derby. W. B. MATTHEWS.

ANKARA CATS

SIR,—Dr. Smithells (Sept. 19), who was interested to learn that Ankara white cats with variously coloured eyes are congenitally deaf, and likened the condition to Waardenburg's syndrome, might like to know that there is a long history of published observations on white cats and deafness, beginning as early as 1828, and including Darwin along the way.

In modern times, a good discussion of the matter was given by Ruth Bamber,[9] with a later note by C. C. Little.[10] The three factors of coat colour, eye pigment, and hearing ability in their various permutations exhibit a considerable degree of correlation. Bamber says "the correlation is evidently between all

1. McQuarrie, I. *Amer. J. Dis. Child.* 1954, **87**, 399.
2. Cochrane, W. A., Payne, W. W., Simkiss, M. J., Woolf, L. I. *J. clin. Invest.* 1956, **35**, 411.
3. Kinsbourne, M., Woolf, L. I. *Arch. Dis. Childh.* 1959, **34**, 166.
4. Sherman, H. *Amer. J. Dis. Child.* 1947, **74**, 58.
5. Geppert, L. J., Spencer, W. A., Richmond, A. M. *J. Pediat.* 1950, **37**, 1.
6. Ulstrom, R. A., Ziegler, M. R., Doeden, D., McQuarrie, I, *Metabolism.* 1952, **1**, 291.
7. Engelhardt, J., Kraayenbrink, K., Villeneuve, V. H. de. *Maandschr. Kindergeneesk.* 1955, **23**, 85.
8. Middleton, J. E. *Brit. med. J.* 1959, i, 824.
9. *J. Genet.* 1933, **27**, 407.
10. *Nature, Lond.* 1934, **133**, 215.

three characters, not between any two, but it is by no means perfect". And again, "both the blue eyes and the deafness are intimately associated with *dominant* white coat color"—i.e., not albino.

Dorothy Wolff [11] gave a histological report on inner-ear pathology, and said all her deaf cats were non-albino white with blue eyes. This information might also be of interest to research otologists.

Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. JOAN STAATS.

A CARDIAC DEFIBRILLATOR: A WARNING

SIR,—I think that a few comments should be made about the safety of the defibrillator described by Dr. Lucas (Aug. 22).

He implies that if 1-amp fuses are connected in a circuit, the current amplitude will be limited to 1 amp., and the time for which it flows will be limited to 0·2 sec. This, unfortunately, is not so. The Belling-Lee standard cartridge fuse-link rated at 1 amp., for example, is designed to operate continuously at 1 amp., and to have a *minimum* fusing current in the region of 2 amp. It can pass far higher currents than this, although the fusing time will then be less. The current in a defibrillating circuit is determined chiefly by the impedance of the heart and the area of contact of the electrodes. Thus, if 1-amp fuses are used, it is quite possible for currents of nearly 2 amp to pass for as long as the press-button switch is depressed; on the other hand, a current of, say, 3 amp may pass for 0·1 sec.

When a circuit is doubly fused, as is that of the emergency defibrillator, it is not usual for both fuses to blow, unless the current is very much higher than the fuse rating. If the fuse which blows happens to be in the neutral side of the mains, the live side will be left connected to the patient for as long as the press-button switch is depressed.

Thus, there exists the possibility not only that neither fuse may blow, but that only one may blow. Consequently, there are two sources of danger in the use of this apparatus, which are not evident from its description: the patient might be burned by the continued application of currents up to 2 amp, and electrocution of the patient or medical personnel might result from the live side of the mains remaining connected *unknown to the operator*.

In order for apparatus of this kind to be safe, it should have a mains isolating transformer, as McMillan [12] has mentioned, and a controlled time switch. If the emergency defibrillator is used, it would be wiser simply to depress the switch very briefly, rather than to rely on the fuse action.

Nuffield Institute for Medical Research, Oxford D. G. WYATT.

SIR,—I have read with apprehension Dr. Lucas' account of a simple cardiac defibrillator, and feel I should hasten to issue a warning. This apparatus as described is dangerous and could be lethal not only to the surgeon, but to anybody handling it or the patient.

It is normal practice for one wire of the electric mains to be earthed, and it would be quite possible for the anæsthetist, or assistant in contact with the patient or some part of the operating-table, to receive a fatal shock under certain easily attained circumstances. While I agree that as far as the patient is concerned the provision of the fuses is a crude safeguard, in that they would probably blow out in the time stated, this is dependent on the fact that the resistance to be expected is of the order of 50 ohms, and a sufficiently large current would flow to blow the fuses in a short time. However, if a contact were made between one electrode and earth with a person as the connection, it is quite likely that the effective resistance would exceed 240 ohms, in which case there would be no safety factor, and a fatal shock could easily result.

I have studied the problem of defibrillator construction, and cannot too strongly emphasise that any such apparatus which does not use a transformer must be condemned, and even with a transformer there are certain other safeguards which should be incorporated.

I have in preparation a paper which I intend to submit to the *Medical Journal of Australia*, setting out all the factors involved, and details of a simple and safe unit which can easily be reproduced at small cost.

Hobart, Tasmania. K. MELVILLE KELLY.

*** We asked Dr. Lucas about the safety of the defibrillator and his reply follows.—ED. L.

SIR,—It has been pointed out to me that this apparatus does not conform with the Ministry of Health's safety regulations for hospitals, since, under certain circumstances, an onlooker in contact with the patient could receive an electric shock. For example:

(1) If a second shock is given after the first one without changing the fuses it is conceivable that the first shock will have only blown the neutral fuse. If this did occur the patient would be live and could short to earth via an onlooker who was in contact with him (it could, of course, happen during the first shock if the button switch were depressed continuously).

(2) If the blades were touched inadvertently or the insulation became faulty.

To reduce these risks I would suggest that instructions 2, 3, and 4 on the back of the apparatus be altered to read:

(2) Wet electrodes, and place on either side of the ventricles. Whenever possible the operator should wear rubber gloves and should be the only person in contact with the patient.

(3) Press button momentarily only. Do not hold down.

(4) Remove *both* active fuses and replace with two reserve fuses. It is vital that this be done after each time the button has been depressed.

I wish to stress again that this apparatus is for emergency use only. It was designed to be made as cheaply as possible so that large numbers could be readily available in hospitals for every possible situation where cardiac arrest might occur. It is recognised that this device, because of its cheapness, is potentially dangerous, so the risk of its use must be weighed against its possible value in saving a life.

Surgical Unit, University College Hospital Medical School, London, W.C.1. B. G. B. LUCAS.

ÆTIOLOGY OF PICA

SIR,—I should like to comment on the statement in your annotation of Sept. 5 that "a child seeks, by a primitive instinct, to supplement its iron stores by eating earth and clay, which sometimes contain *some* elemental iron." Further work on this subject has revealed that the objects selectively eaten by these children with pica contain considerable iron.

In my article [1] I recorded that whereas wood, black soil, and clay were occasionally eaten the major predilection was for sand. The parents were asked to bring samples of the sand, soils, and clays eaten by their children and random specimens were submitted for chemical analysis. Muller [2] reported finding that the content of iron as Fe_2O_3 in these samples

11. *J. Hered.* 1942, **33**, 39.
12. McMillan, I. K. R. *Brit. med. Bull.* 1955, **11**, 232.

1. Lanzkowsky, P. *Arch. Dis. Childh.* 1959, **34**, 140.
2. Muller, J. Personal communication, 1959.

ranged from 0·38% up to 1·04%. Fuller,[3] of the department of geology of the University of Cape Town, commented on the fact that the soils and clay in the area from which the patients with pica came are known to have such a high iron content that it has not been possible to establish ceramic and other pottery industries in that region. Fuller stated that in his experience the soils and sand contained from a trace up to 40%, with an average of a few per cent, of iron oxide and iron hydroxide. Gastric juice pH would probably be adequate for solution to occur. It appears that children with iron-deficiency anæmia and pica instinctively or unwittingly select for ingestion mainly substances with a relatively high iron content.

I should also like to mention that in the article I recorded successful treatment of pica with oral iron and not, as stated in your annotation, that *all* my cases were treated with parenteral iron. Furthermore, I have seen a considerable number of cases of pica, since the publication of my article, many of which have been cured by oral iron.

Department of Child Health, University of Cape Town and Red Cross War Memorial Children's Hospital, Cape Town. PHILIP LANZKOWSKY.

*** Last week (p. 569) Dr. Carlander reported that of some 100 patients he had seen with pica, all had a low serum-iron level.—ED. L.

ULCERATIVE COLITIS AND CARCINOMA COLI

SIR,—Rosenqvist et al.[4] referred to the experience of some physicians with the problem of ulcerative colitis and carcinoma. The statistics they gave represent a small series of 150 patients with chronic ulcerative colitis. Of the 150, 8 developed carcinoma—an incidence of 5·3% for the whole group. This group then is subdivided by periods of observation. There were 8 patients of 59 observed from 11 to 22 years who developed carcinoma—an incidence 13·5%. This is further broken down into a group of 24 patients observed for 15 to 22 years, of whom 7 developed carcinoma for an incidence of 29·1%. These groups are too small to yield statistically significant results. We cannot find proof in this article of the authors' statement that " among patients who have had ulcerative colitis for ten to twenty years, 1 in 3 develops carcinoma of the colon ". They also state that out of a total of 500 patients, cancer developed in 26. This seems to be an incidence of 5·2%, which would be in line with our own experiences,[5–10] and those of many other investigators.

In a group of 2000 patients with ulcerative colitis observed between the years of 1913 and 1938 and reported in 1954 the incidence was indeed 5%. It is true that when ulcerative colitis occurs in the first or second decade of life that the incidence of carcinoma is apt to be higher than if the ulcerative colitis develops in the later years of life. The incidence of carcinoma among the younger individuals still represents a portion of the 5%. It is important to follow these patients very carefully and have them examined periodically. Careful, periodic (semi-annual or annual) reassessment of each individual with longstanding chronic ulcerative colitis, to include proctoscopy and roentgenological examination, seems preferable to a tremendous increase of patients who have had total colectomy.

3. Fuller, A. C. Personal communication, 1959.
4. Rosenqvist, H., Öhrling, H., Lagercrantz, R., Edling, N. *Lancet*, 1959, i, 906.
5. Bargen, J. A. *Arch. Surg.* 1928, **17**, 561.
6. Bargen, J. A. *New Engl. J. Med.* 1934, **210**, 692.
7. Sauer, W. G., Bargen, J. A. *Proc. Mayo Clin.* 1944, **19**, 311.
8. Sauer, W. G., Bargen, J. A. *J. Amer. med. Ass.* 1949, **141**, 982.
9. Bargen, J. A., Sauer, W. G., Sloan, W. P., Gage, R. P. *Gastroenterology*, 1954, **26**, 32.
10. Bargen, J. A., Gage, R. P. 65th Annual Meeting of the Association of Life Insurance Medical Directors of America, October, 1957.

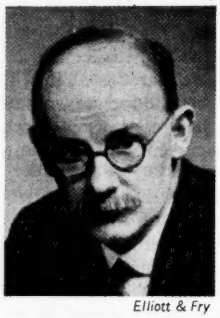
According to the present state of our experience and knowledge, there is no need to consider a prophylactic colectomy for ulcerative colitis in order that carcinoma may be prevented in the future. Perhaps in some instances ileorectostomy could be accomplished, but then the rectum remains as the potential source for the development of cancer, and surely, in most instances, ileostomy with all its hazards would be indicated if colectomy were performed.

Mayo Clinic, Rochester, Minnesota. J. A. BARGEN
WM. G. SAUER.

Obituary

ROBERT RUTSON JAMES
F.R.C.S.

Mr. Rutson James, whose death on Sept. 28 we announced last week, was consulting ophthalmic surgeon to St. George's Hospital and for over twenty years editor of the *British Journal of Ophthalmology*.


Elliott & Fry

He was born in 1881 in a west country parsonage, and was educated at Winchester College. He qualified from St. George's Hospital in 1905 and the following year gained the F.R.C.S. After holding house-appointments at St. George's Hospital, he worked at Moorfields Eye Hospital under Mr. William Lang and Sir John Parsons and at the Royal Westminster Ophthalmic Hospital under Brewerton and MacMullen. In 1909 he was appointed to the consulting staff of St. George's Hospital at the age of 28, and he became dean of the medical school after the 1914–18 war.

From 1924 to 1948 he was editor of the *British Journal of Ophthalmology*, and from 1939 to 1945 of the *Transactions of the Ophthalmological Society of the United Kingdom*. He had already served the society as secretary (1915–21) and as Bowman librarian (1924–27), and his work was recognised by his election as an honorary member. Throughout his life he retained a love of classical literature, history, and archæology. His *Studies in the History of Ophthalmology in England prior to* 1800 *A.D.* was an admirable piece of historical research.

H. B. S. writes:

" Rutson James' childhood experiences in observing parental management of village folk and their problems contributed much to his humanity, his constant and sensitive consideration for the feelings of others, his abounding patience, and kindness.

His courtesy, always so genuine, was constant whoever he addressed, from the humblest illiterate hospital patient to the exalted intelligentsia in his private practice. As an eye surgeon he was meticulous and in his clinical work his powers of observation were acute, shrewd and accurate at a time when the instrumental aids to the minute examination of the eye were simple and less elaborate than today. Shy, hypersensitive, and retiring he preferred to have a small private practice of devoted patients. It was probably the inevitable stresses of surgical work which caused him to retire prematurely from his hospital appointment and practice to seek a happy retreat among his books. His own writings were in impeccable English and his annotations charged with whimsical wit. He was an admirable doctor, a perfect gentleman, a generous and lovable friend."

Mr. Rutson James is survived by a daughter.

Notes and News

ON THE WAITING-LIST

ACCORDING to official records the number of elderly people in England and Wales awaiting admission to hospital has remained fairly constant since 1949. But this constancy may be more apparent than real, and, in the view of the Hospital Aid Service for the Elderly,[1] hospital waiting-lists are dangerously misleading. The information they have gathered during 1958 while visiting, on behalf of the Metropolitan hospitals, old people awaiting admission suggests that the figures on which the waiting-lists are based are often unreal. They found that among the 675 chronic sick patients who were on the waiting-lists of ten hospital groups in or on the borders of greater London 187 had already been admitted to some hospital. Perhaps they were not in the most suitable beds, but they were in fact being cared for by the hospital service. The unreality of these lists was further shown by a detailed inquiry into the exact condition of 8 patients who were among those said to be awaiting transfer from welfare authority accommodation. In fact 3 had died, 3 had been admitted to other hospitals, and 2 had recovered.

These bald statistical summaries, the service point out, do not show the distress caused to elderly people and their relatives by some hospitals' practice of putting on their waiting-list patients whom they do not really expect to admit. At the time it may seem easier to say that an old person is being put on the waiting-list rather than to admit frankly that unless his social or medical condition alters it is improbable that a hospital bed will be found for him. In fact this kindly subterfuge too often means that the old person and his relatives go without practical help from the domiciliary services or other organisations. The service was able in 1958 to arrange alternative help of this kind for 19% of the 2400 patients they visited. Usually these arrangements enabled the patient to remain comfortably at home. In the experience of the service, most young people dislike " putting away " an elderly relative and if they are offered some help—perhaps a piece of simple nursing equipment such as a hoist—they are anxious to continue looking after him. Well-intentioned but illusory promises of admission to a " hospital in Spain " does not only deprive the patient of more limited but immediate help; it also gives the discouraging impression that to provide adequate care for the elderly is a greater problem than in fact it is. Hospital beds should be kept for those who are likely to respond to hospital treatment and those needing care which can only reasonably be given in hospital. They are not always the best form of care for an old person. The service wonders if the waiting-list, and even at times hospital beds, are not sometimes used because it is easier " than to seek the alternative ".

HEALTH VISITING SERVICE

THE Ministers of Health and Education, in consultation with local-authority and professional associations, have had under consideration the report of the working party on health visiting,[2] and they have now issued a circular [3] giving their views. They are in general agreement with the recommendations in the report, and in particular accept the need in appropriate cases for a new grade of group adviser. The Ministers particularly draw attention to the advantages to families, and to the service as a whole, of health visitors combining work in both the maternity and child-welfare and school health services, and to the contribution health visitors can make, with hospitals and general practitioners, in giving health education and social advice in their homes to patients with physical and mental illness. The Ministers feel that it is important that the health visitor should, as far as possible, be relieved of duties in the school health service and at maternity and child-welfare clinics which do not call for the use of her special skills, so that she should be able to concentrate on giving health education and advice. They also strongly endorse the working party's recommendations for a close association between the health visitor and the general practitioner, and hope that authorities will continue to take active steps to encourage this. The attachment of a health visitor to a group of practitioners has been found to work successfully. Liaison with hospital staffs, both nursing and social workers, should be developed, especially for visitors who have young children and old people in their care.

1. Report for 1958 of the Hospital Personal Aid Service for the Elderly (c/o New Cross General Hospital, Avonley Road, London, S.E.14).
2. See *Lancet*, 1956, i, 908.
3. 26/59.

SHORTAGE OF DIETITIANS

THE British Dietetic Association set up a fact-finding committee of members to inquire into the shortage of dietitians, particularly in the National Health Service. The committee's interim report says that a questionnaire was sent to 314 hospital management committees and boards of governors of teaching hospitals in the United Kingdom, asking for information on the employment of dietitians as at Aug. 1, 1959. The 257 replies received showed that in 100 groups of hospitals no dietitians were employed; in the other 157 groups the picture was as follows:

	Posts filled	*Posts vacant*	*Total posts available*
Therapeutic dietitians (full-time) ..	202	84	286
Therapeutic dietitians (part-time) ..	28	10	38
Dietitian/catering officers	22	2	24
Totals	252	96	348

In the 57 groups from whom no reply was received no information was available about 15 of them. In the other 42 groups the records of the British Dietetic Association showed that in 24 groups no dietitians were employed and that in the remaining 18 the position was as follows:

	Posts filled	*Posts vacant*	*Total posts available*
Therapeutic dietitians (full-time) ..	20	15	35
Therapeutic dietitians (part-time) ..	4	1	5
Dietitian/catering officers	3	..	3
Totals ..	27	16	43

Thus, in a total of 391 posts available for dietitians in the National Health Service 112 remain unfilled.

The number of students qualifying as dietitians in the past five years, up to March 1 each year, is as follows:

1955	44
1956	39
1957	43
1958	42
1959	45

A questionnaire was also sent to some 740 full members of the Association at home and overseas, but the analysis of the replies to these has not yet been completed.

SOCIAL CARE OF DISSEMINATED SCLEROSIS

MUCH can now be done to improve the lot of patients with disseminated sclerosis, and in his address at the annual meeting of the Multiple Sclerosis Society, held last June, Sir Selwyn Selwyn-Clarke spoke of the social care of the disease. He appealed both to the Ministry of Health and to hospital management committees to avoid the nursing of young hospital patients for long periods in the same wards or dayrooms as the very old. The patient with this disease needs to be treated as far as possible as a normal person, and whenever his physical state and his home conditions permit he is best allowed to live at home among his family—" perhaps being readmitted to hospital from time to time for a check-up and to give his relations a ' breather ', as it were, if he requires much and constant assistance in washing, dressing, moving about, or taking his meals ". He must be helped to help himself, even if it is a real struggle for him to do things, and must try to keep up his interest in his work, pastimes, and contacts with other people.

Under the National Assistance Act, Sir Selwyn pointed out, many forms of practical help may be available.

" Take, for example, a patient who has lost the use of his legs and may have been supplied with a wheel-chair through the hospital services. This may mean that structural adaptations and aids to living of various kinds are required in his home, such as the replace-

ment of doorsteps by an inclined plinth, the widening of a doorway, the construction of a french window on the ground floor or of rails in the water-closet and bathroom, or gadgets to help a disabled housewife in the kitchen. The welfare officer may also be able to arrange for attendance at a craft centre or sheltered workshop, if appropriate, or at a club or other social activity. Gadgets for putting on shoes and stockings, for washing, eating, drinking, and the use of tools can usually be obtained through the local branch of the British Red Cross Society or other voluntary organisations for the handicapped."

Referring to the voluntary and religious organisations whose members devote themselves to the welfare of patients, Sir Selwyn welcomed the formation, in some areas, of associations of the statutory and voluntary organisations concerned with the handicapped, as described in Dr. J. H. Nicholson's recent survey *Help for the Handicapped*. He thought it would be useful to multiply the society's representatives and local branches even in small out-of-the-way places, so as to offer help, interest, and friendship especially to those living alone; and he concluded with a suggestion that wherever a branch is formed the medical officer of health of the locality should be invited to join it.

University of Birmingham

The following appointments have been made:

Mr. Geoffrey Slaney, senior lecturer in surgery; Dr. June K. Lloyd, lecturer in paediatrics and child health; Dr. P. W. Dykes, lecturer in medical biochemistry and experimental pathology, department of experimental pathology; and Dr. I. M. Leck, lecturer in social medicine.

University of Liverpool

Dr. J. C. Davis has been appointed senior lecturer in endocrine pathology.

Royal College of Physicians of London

On Thursday, Nov. 5, at 5 P.M., at the college, Pall Mall East, S.W.1, Dr. Alan Kekwick will give the Bradshaw lecture. His subject will be On Adiposity.

Royal College of Surgeons of England

At a meeting of the council on October 8, with Sir James Paterson Ross, the president, in the chair, Prof. M. A. Rushton was admitted to the council as a coopted member representing dental surgery. Prof. R. S. Pilcher was admitted to the Court of Examiners.

A diploma of fellowship was granted to P. J. Carter, and diplomas of membership to L. P. Connolly, K. S. A. Madgwick, and R. P. Golding.

Diplomas of fellowship in the Faculty of Anæsthetists were granted to the following:

F. J. Davis, M. E. Tunstall, R. C. Brookes, Pamela M. Ordish, G. D. Parbrook, C. B. Franklin, J. S. Toner, Murari Mohon Som, J. E. Briffa, John Fraser-Jones, Mendel Levitt, Lorna Chippindale, M. J. Egginton, Joseph Greenan, Nazir Ahmed, H. I. A. Nisbet, Upali Weerackody, Joan D. A. Casserley, Michael Cooke, Lois R. Davidson, E. P. Fitton, D. R. Ball, E. D. L. Bennett, T. H. L. Bryson, L. C. Fernando, Phillida M. Frost, J. G. Morgan, John Wilson, P. V. Cole, Margaret C. Holderness, P. F. Knight, Frank Fisher, J. C. Stoddart.

The following diplomas were granted jointly with the Royal College of Physicians:

D.O.—T. L. F. Aung Than Averill, K. L. Batten, M. J. A. Britten, W. H. Clarke, Anthea M. S. Connell, Mohamed Sherif Dawood, Arnold Freedman, Ranendra Nath Ghosh, Mohamed El Sayed Ibrahim, E. O. Jacobs, B. S. Jay, Shaikh Mohammed Kamaluddin, T. D. Leckie, R. D. Loudon, D. J. McAuliffe, J. von L. Malan, Khalida Naib, Ramajois Srekantian Nanjundaswamy, Jean A. Peachey, J. F. Pereira, R. J. Pyne, N. S. C. Rice, I. F. Robertson, P. V. Rycroft, Mohamed Osman Sheriff, Syed Mohd Siddique, Iqbal Singh, David Staig, W. E. Staples, J. M. Straiton, F. P. Sullivan, Rajeshwar Prasad Tandon, J. N. Taylor, Tha Khin, Peter Wright.

D.Phys.Med.—J. R. Burrows, Leslie Koadlow, L. H. Truelove, P. K. B. White.

D.T.M. & H.—Syed Hamid Ali, Dharma Prakash Arya, John Barnes, Hildegard Birkhahn, R. J. P. Blyth, Eswarappa Gowd Budiyappa, D. M. Devane, Abbas Hasanally Dossal, Mohammed Ehtishamuddin, Parviz Faridian Aragh, Syed Mohammad Faruque, M. D. Goulding, Mohammed Abdul Halim, A. G. Harwood, Mohammad Fakhrul Hasan, D. S. Hutton, Prem Narayan Jha, J. S. Karcher, Husain Ali Khan, Musheer Ahmad Khan, E. P. Lawrence, Wan-Yee Lo, Maitray Markandrai Mehta, G. G. Meilland, F. W. Murphy, Kanubhai Gordhanbhai Patel, Lalitkumar Chaturbhai Patel, Shivnandan Prasad Rastogi, Mohammad Raza, Hilary M. Rowson, Imdadali Badruddin Sardharwalla, Ghulam Sarwar Sethi, Nizamuddin Ziauddin Shaikh, Abdus Samad Shera, Achyut Bahadur Shrestha, Jamil Ahmad Siddiqui, W. G. Strauss, C. R. Tribe, D. M. Wayte, H. W. Whittingham, D. N. Wysham, Lois R. Zimmerman.

University of Edinburgh

On July 13 the following degrees and diplomas were conferred:

M.D.—*G. M. Carstairs, P. N. Edmunds, J. F. McHarg, D. E. B Powell (commended); D. B. Scott, *G. H. M. Thornton.

Ch.M.—*H. D. Ritchie, H. B. Torrance (gold medal for thesis).

D.Sc.—J. A. Loraine.

Ph.D.—Padmadhar Bhuyan, R. B. Cross, *Salonas Hassan Ismail, Inayat Khan, A. E. Stuart.

M.B., Ch.B.—H. G. Coore, J. H. Turner (with honours); Elinor Adam, A. C. A. Alexander, J. L. S. Alexander, Kosin Amatayakul, V. B. G. Amu, J. L. Anderton, R. W. Archibald, D. T. Baird, E. E. Barnard, D. G. D. Barr, D. S. G. Bath, P. W. D. Berry, J. L. Boak, F. A. Boddy, R. A. Bowie, Elizabeth M. W. Bradford, S. H. Brock, E. G. Buchanan, J. C. Burn, W. R. Cameron, Dorothy O. Campbell, Michael Clare, R. L. Clark, Forrester Cockburn, J. J. C. Cormack, A. B. Craddock, A. L. Crombie, G. K. Crompton, Christine E. J. Dandie, J. W. Delaney, M. J. Dell, A. W. Dellipiani, Mary E. Dewar, A. J. Dougall, Alexander Dumbreck, C. R. Dundas, H. P. Ferrer, Allan Forsyth, Bernadette A. Gallagher, N. R. Galloway, P. F. Gibson, T. G. Girdwood, Bin Sin Goh, George Gordon, Jessie Gordon, J. A. Gray, Alison F. Grieve, Michael Grundy, Andrew Gunn, A. W. Harcus, L. J. Hastewell, R. D. Henderson, B. F. Heywood, Gillian Hindley, W. J. M. Hood, George Horsburgh, A. W. Howarth, P. W. Kershaw, T. K. C. King, Mary Kinghorn, Edith McL. Lamont, Kathleen G. Large, David Lees, Lorna J. Lees, J. G. Lenson, A. G. Livingstone, P. A. Loynds, J. M. Lynch, Gwendyth A. McAlpine, Desmond McCann, Angus Macdonald, S. W. MacGregor, John McKendrick, Eileen B. Mackenzie, Marjory G. McK. McKinnon, C. E. Mackintosh, M. S. F. McLachlan, T. K. Maclachlan, M. J. MacLean, C. McG. Mailer, C. M. Malone, D. N. S. Malone, A. G. Maran, G. R. Massarella, M. J. Mellor, G. T. Millar, Genevra M. Mitchell, T. O. Mulligan, Ronald Mulroy, Lilian E. Murchison, K. N. Murray, Margaret L. S. Murray, Barrie Newton, Babu Narayana Panikker, Shirley R. Patterson, Margaret E. Pawson, J. K. Peden, Janet A. Peters, C. A. Phillips, Minnie W. Pollard, R. F. Pottinger, Andrew Ramsay, I. D. Ramsay, R. G. Rangecroft, A. K. Ravenscroft, Patricia M. Rebbeck, J. A. Redman, B. J. Ricci, Isobel A. Ritchie, I. W. Percy-Robb, R. M. Rowan, C. V. Ruckley, D. M. Scruby, E. R. Seiler, Sydney Selwyn, B. W. Serpell, W. I. H. Shedden, Ann I. Simpson, C. A. Simpson, M. M. Simpson, R. D. C. Sinclair, R. A. Sleet, D. J. C. Sneddon, R. T. Steele, R. E Steward, Anant Tejavej, I. C. Thomson, G. Kwong Hong Tsang, A. M. Tulloch, J. G. Turnbull, F. W. Turner, Etim Elijah Udoh, Anne M. Urquhart, D. D. Walker, J. G. Walker, Joan Wallace, W. L. White, John Williamson, Catherine D. Wilson, K. M. Wood, D. G. Wray, A. K. Zealley.

B.Sc.—George Philp (with honours).

D.P.H.—A. McI. Anderson, Anne J. Anderson, T. G. Behan, G. M. A. H. Bernard-La Pommeray, C. H. James, Vedast Kyalakishaija Kyaruzi, W. E. Laufer, J. A. MacDougall, Marian F. Natkanski, G. S. C. Nzegwu, John Oliver, Sheila G. Quain, I. F. Ralph, Alexander Watt.

D.P.M.—A. H. C. Sinclair-Gieben.

D.T.M. & H.—Muhammad Fakhrul Azam, Khushbir Singh Bedi, Susanta Kumar Datta, Ekpo Etim Inyang, G. C. Irvine, Kottaram Venkatachala Sarma Krishna Das, Madhusudan Shrinivas Mahuli, Brajjeshwar Mittra, Derek Ogston, Nanu Kuttymenon Purushothaman.

* in absentia.

Prof. K. W. Donald will give his inaugural lecture on Monday, Oct. 19, at 5 P.M., in the University New Buildings, Teviot Place, Edinburgh. He will speak on research and clinical medicine.

University of St. Andrews

Dr. J. A. R. Lenman has been appointed senior lecturer in neurology in the department of medicine, Queen's College, Dundee.

On Oct. 7 the degree of M.D. was conferred on I. H. Redhead.

University of the Witwatersrand

Prof. E. H. Cluver is retiring from the directorship of the South African Institute for Medical Research to take up the post of dean of the faculty of medicine in the university.

Wellcome Trust

Grants totalling over £400,000 were made by this Trust during the year ended Aug. 31, 1959. They included:

University of Cambridge.—Up to £120,000 to extend research accommodation in the department of biochemistry; up to £60,000 to provide new laboratories in the department of radiotherapeutics.

Royal Infirmary, Manchester.—Up to £30,000 to provide a metabolic research unit.

University and City Hospital, Edinburgh.—Up to £28,000 to build a respiratory-diseases research unit.

University of Oxford.—Up to £11,500 to provide an ultracentrifuge and micro-electrophoresis equipment in the Dunn school of pathology.

University of East Africa, Makerere College.—Up to £12,500 to provide a mobile laboratory and an animal house in the department of physiology.

McGill University, Montreal.—Up to £13,000 to provide an electron microscope in the department of physiology.

Grants totalling £42,500 for research assistance or expenses were made to individuals and 116 research travel grants were awarded at an overall cost of £22,000.

Association of Clinical Biochemists

The following officers have been elected:

President, Dr. C. P. Stewart; chairman, Dr. A. L. Latner; hon. treasurer, Dr. J. H. Wilkinson; hon. secretary, Dr. A. L. Tárnoky (Royal Berkshire Hospital, Reading).

Postgraduate Travelling Fellowships

The British Postgraduate Medical Federation invites applications for these fellowships from medical or dental graduates who are training as specialists and who wish to study methods of practice, education, and research at universities or other centres in the United Kingdom and abroad. Particulars will be found in our advertisement columns.

Scottish Hospital Endowments Research Trust

The following have been appointed to the advisory committee of this Trust in succession to members who have retired: Prof. J. H. F. Brotherston, Prof. J. N. Davidson, Prof. R. B. Hunter, Prof. Alexander Macdonald, and Prof. G. L. Montgomery.

Triple Qualification Board of Scotland

The following have been granted the diploma of licentiate of the Royal Colleges of Physicians and Surgeons of Edinburgh and the Royal Faculty of Physicians and Surgeons of Glasgow:

Ali Hassan Karimbux Brohi, W. E. St. C. Crosbie, Isabella Gal, Dezso Schachter, Istvan Varga-Toth, Bik-May Wai.

Association of Industrial Medical Officers

A meeting of this Association will be held on Oct. 30 and 31 at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, and King's College Hospital, Denmark Hill, S.E.5. Dr. C. L. Sutherland will give the Hubert Wyers lecture, entitled Pneumoconiosis, and other speakers will include Dr. V. C. Medvei, Dr. F. W. Meichen, and Dr. J. B. Harman. Further particulars may be had from the secretary of the Association at 47, Lincoln's Inn Fields, W.C.2.

Journal of the American Medical Association

Dr. John H. Talbott has been appointed director of the division of scientific publications of the American Medical Association and editor of its *Journal*.

Dr. Talbott was born at Grinnell, Iowa, in 1902, and qualified from Harvard Medical School in 1929. After an internship at Columbia-Presbyterian Medical Center, New York, he returned to Massachusetts General Hospital, Boston, in 1931. He remained there until 1946, except for his five years' Army service. From 1943 to 1946 as a colonel he was chief of laboratory services of the Sixth General Hospital and commanding officer of the Climatic Research Laboratory, Lawrence, Mass., for which he was made a member of the Legion of Merit. Since 1946 Dr. Talbott has been physician in chief, Buffalo General Hospital, and professor of medicine at Buffalo Medical School. For nine years he has been editor of *Medicine*.

Dr. Johnson F. Hammond, for many years associate editor of the *Journal of the American Medical Association* and acting editor since the retirement of Dr. Austin Smith nearly a year ago, now retires and becomes editor emeritus.

Royal Medical Benevolent Fund

In presenting his report for 1958 at the annual general meeting of this Fund on Sept. 30, Dr. Anwyl Davies, the hon. secretary, said that, though the year had seen the coming into force of the National Health Service pensions, the number of new applications for help had risen by over 20 on the previous year, and the total sum disbursed in grants alone showed a rise of over £4000 to £34,202. There were still many doctors and their widows who, by reason of their age, were outside the scope of the National Health Service and National Insurance benefits, and others, such as widows with families to maintain and educate, who needed their State aid to be supplemented. Mainly as a result of this ever-increasing number of requests for help, the year's accounts showed a deficit of expenditure over income of £3893, and he appealed again to all in more fortunate circumstances to subscribe something, however small, to the Fund.

Sir Henry Tidy was re-elected president, Mr. F. A. Juler hon. treasurer, and Dr. Anwyl Davies hon. secretary. During the year the Fund moved to its new office at 37, St. George's Road, Wimbledon, London, S.W.19.

Tools of Biological Research

The second symposium with this title was held at Guy's Hospital on Oct. 2 and 3. It was organised by the department of surgery and was a sequel to the successful meeting last year (*Lancet*, 1958, ii, 856). Lord Cohen of Birkenhead gave the opening address.

Pure Food Centenary

A conference will be held in London from Sept. 20 to 23, 1960, to celebrate the centenary of the Act for preventing the adulteration of articles of food and drink. Further particulars may be had from the secretariat, Pure Food Centenary, 14, Belgrave Square, W.1.

Medical Protection Society

Dr. F. Harwood Stevenson, chairman of council, presided over the annual meeting of this society on Oct. 7, in the absence of the president, Sir Ernest Rock Carling, who was indisposed. Dr. Harwood Stevenson was able to report that the society had had a satisfactory year. Membership had once more risen and now stood at a new maximum of 35,000. Income had exceeded expenditure by £6000, and in these propitious circumstances there was no need to consider raising the annual subscription of £2. Incidentally, he added, to obtain comparable cover in many parts of the Western World a doctor might have to pay fifty to a hundred times as much. Dr. Harwood Stevenson went on to say that this was the last time that the society would meet in their present friendly but cramped home. They had been fortunate in acquiring on a long lease the premises at 50, Hallam Street, formerly occupied by the General Dental Council, and they hoped to move to their new quarters before the end of this year.

The meeting passed a special resolution making minor alterations in the society's constitution, which would facilitate dealing with claims involving a hospital authority as well as a member according to the policy agreed between the Ministry of Health and all the defence organisations.

The income of the society for the year was £86,792—an increase of £4337 over last year. In addition £3542 indemnity claims had been recovered from underwriters for previous years. Expenditure for the year was £80,592—a decrease of £6335. The funds available for the protection and defence of members' interests now exceed £236,000.

The society's officers were re-elected—Sir Ernest Rock Carling as president, Mr. W. M. Mollison as treasurer, and Dr. A. R. French as secretary. The chairman of council is Dr. Harwood Stevenson, and the deputy secretary Dr. H. A. Constable. The offices, from which the latest annual report may be obtained, are for the present still at Victory House, Leicester Square, London, W.C.2.

Sir Solly Zuckerman has been appointed scientific adviser to the Minister of Defence and chairman of the Defence Research Policy Committee. The appointment is a full-time one and will be for five years. Sir Solly will retain his Sands Cox professorship in anatomy at Birmingham University on an honorary basis and will be available to the university for consultation.

Dr. J. H. Douglas Webster has been elected to the committee of the Foundation for the Study of Cycles, New York, as its first medical member.

The Berkshire Association for Mentally Handicapped Children are holding a conference on the education and training of mentally handicapped children on Saturday, March 19, at Reading University. Sir John Wolfenden will give the opening address. Further information may be had from Dr. Maurice Brook, Lower Village Road, Sunninghill, Ascot.

Bronchial Asthma—The Chest and Heart Association have published a report of a meeting on this subject held in London on Feb. 25. Copies (12*s*. 6*d*.) may be had from the Association, Tavistock House North, London, W.C.1.

The American Heart Association has published a guide for parents, *The Home Care of the Child with Rheumatic Fever*. This attractive, well-produced booklet gives sensible advice, which will usefully reinforce and amplify the doctor's words. More could have been said about convalescence, but the importance of prophylaxis is clearly pointed out. Copies may be had from the Association, 44, East 23rd Street, New York 10, N.Y., U.S.A.

Cambridge University Medical School is holding symposia for general practitioners at Cambridge, Norwich, Ely, and Ipswich during the session. The first, on respiratory diseases, will begin on Saturday, Oct. 31. Particulars may be had from the secretary of the medical school, Tennis Court Road, Cambridge.

An endocrine demonstration on gigantism and acromegaly will be given at Guy's Hospital, London, S.E.1, on Monday, Oct. 26, at 5 P.M.

The subject for the National Varicose Foundation's silver medal this year is the Cause and Care of the Post-thrombotic Leg. Further particulars may be had from the Foundation, 5, Park Lane, Wembley, Middlesex.

This year 10 scholarships have been awarded by the British Commonwealth Nurses War Memorial Fund, bringing the total now awarded to 94. The offices of the Fund are at Dorset House, Stamford Street, London, S.E.1.

The Royal Northern Hospital, London, N.7, will hold its annual clinical exhibition during the week beginning Monday, Oct. 19. The exhibition will be open from 9 A.M. to 9 P.M. daily, and medical films will be shown at 8.30 P.M. each evening.

Mr. E. R. Lawrence has been appointed clerk to the National Health Service Tribunal. Communications should be sent to him at 9, Lincoln's Inn Fields, London, W.C.2.

Diary of the Week

OCT. 18 TO 24

Sunday, 18th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
10.15 A.M. Mr. Anthony Radcliffe: Common Ear, Nose, and Throat Conditions.

Monday, 19th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
3 P.M. Sir Russell Brain: William Harvey, Neurologist. (Harveian oration.)
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Frances Gardner: Aspects of Coronary Artery Disease.
ROYAL FREE HOSPITAL SCHOOL OF MEDICINE, Hunter Street, W.C.1
5.30 P.M. Prof. Harry Dowling (University of Illinois): Long-term Treatment of Bronchiectasis and Chronic Bronchitis with Antibiotics.
INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W.C.1
5.30 P.M. Dr. J. W. Magladery (Baltimore): Certain Neurophysiological Studies of Ageing.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. K. G. Lowe: The Cardiac Catheter as a Tool in Cardiology.

Tuesday, 20th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Pathology.* Dr. M. R. Crompton, Professor Scheidegger (Basle), Dr. P. H. Buxton: Neuropathology.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. R. H. S. Thompson: Biochemistry of Multiple Sclerosis.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. E. H. Belcher: Properties of Radiation.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Frank Denny: Stress Incontinence.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. C. D. Calnan: Allergic Reactions of the Skin.
SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Prof. Douglas Hubble, Mr. C. P. Mayhew, Dr. Emanuel Miller, Dr. W. Linford Rees: Influence of Drugs on Literary Imagination.
SOUTH-WEST LONDON MEDICAL SOCIETY
8.45 P.M. (Bolingbroke Hospital, S.W.11.) Mr. A. M. Desmond: Peripheral Vascular Disease.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. J. B. Cook: Relationship of Spinal Cord Damage to Cervical Spinal Injury.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Dr. J. S. S. Stewart: Cyto-genetical Techniques in the Investigation of Human Intersexes.

Wednesday, 21st

ROYAL SOCIETY OF MEDICINE
5 P.M. *Comparative Medicine.* Mr. M. Crawford: Information and Library Services in Relation to Medical and Veterinary Science. (Presidential address.)
8.15 P.M. *General Practice.* Dr. G. J. V. Crosby: "Rheumatic Diseases" in General Practice. (Valedictory address.)
POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. H. E. de Wardener: Renal Function.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Histology of Normal Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. V. C. Thompson: Diaphragmatic Hernia.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Dr. R. N. Tattersall: Clinical Significance of Tiredness. (Buckston Browne prize essay.)
EUGENICS SOCIETY
5.30 P.M. (Burlington House, Piccadilly, W.1.) Miss Eileen Brooke: Mental Health and the Population.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh, 8
3.30 P.M. Mr. M. F. Nicholls: Behaviour of Tumours.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of medicine, Queen's College, Dundee.) Prof. I. G. W. Hill: Aspects of Electrocardiography including Intracardiac Lead.

Thursday, 22nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4.15 P.M. Dr. Stefan Engel: Evolution of the Mammalian Lung. (Arnott demonstration.)
ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Experimental Medicine and Therapeutics.* Sir Hans Krebs: Biochemical Aspects of Ketosis. (W. E. Dixon lecture.)
8 P.M. *Urology.* Mr. D. S. Poole-Wilson: Occupational Tumours of the Bladder. (Presidential address.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. P. B. Bradley: Neurophysiology of Consciousness.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. F. F. Hellier: Rehabilitation of the Skin Patient.
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Dr. R. Winston Evans: Histogenesis of Ovarian Tumours.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Prof. A. W. Kay: Surgical Experiments in Duodenal Ulcer.

Friday, 23rd

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics.* Prof. J. Caughey, Dr. J. N. Walton, Dr. A. L. Woolf: The Floppy Baby—Infantile Hypotonia.
8.15 P.M. *Obstetrics and Gynæcology.* Dr. Harold Malkin: Observations on Social Conditions, Fertility, and Family Survival in the Past. (Presidential address.)
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Prof. R. S. Pilcher: Surgical Treatment of Angina Pectoris.
4 P.M. Dr. M. D. Milne: Disorders of Potassium Metabolism.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
4.30 P.M. Mr. C. P. Wilson: Vasomotor Catarrhs of the Nose.
INSTITUTE OF NEUROLOGY
4.45 P.M. Dr. G. D. Dawson: Investigations on Sensory Inflow.
UNIVERSITY OF MANCHESTER
5.15 P.M. Prof. A. C. B. Lovell: The Structure of the Universe. (Lloyd Roberts lecture.)

Appointments

BOGER, J. R. F., M.R.C.S.: assistant M.O., Middlesex County Council (area 9).
BURNS, CARL, M.B. Manc., D.P.H., D.C.H.: deputy M.O.H., Burnley.
BURNS, J. C., M.B. Belf., D.P.H.: assistant M.O. and school M.O., Isle of Ely.
CALDWELL, ARTHUR, M.B. Glasg., D.P.H.: M.O.H., Perth and Kinross Joint County Council.
CITRON, K. M., M.D. Lond., M.R.C.P.: consultant physician, Wandsworth chest clinic, London.
GRAINGER, R. G., M.D. Leeds, M.R.C.P., F.F.R., D.M.R.D.: part-time consultant radiologist, United Sheffield Hospitals.
HAVARD, CYRIL, M.CH., B.SC. Wales, F.R.C.S.: consultant in general surgery, Bridgend General Hospital.
HENWOOD, W. R., M.B., B.SC. Wales: assistant M.O.H. and school M.O., Burton-on-Trent.
PINKERTON, I. MADELEINE, M.B. Wales, D.P.H.: senior M.O. for child health, Devon County Council.
ROGERS, F. S., M.B. Leeds: assistant M.O. and school M.O., West Riding of Yorkshire County Council (Shipley division).
SIMMS, O. H., M.B. Sheff., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, United Sheffield Hospitals.
THOMAS, D. W., F.R.C.S.: consultant in general surgery, Merthyr and Aberdare H.M.C.
WHITBY, J. L., M.B. Cantab., M.R.C.P., D.T.M. & H.: consultant bacteriologist, United Birmingham Hospitals.
WILLIAMS, EVAN, M.R.C.S., D.P.H.: assistant M.O. and district M.O.H., Devon County Council (Barnstaple and South Molton).

Leeds Regional Hospital Board:

COLLINS, AGNES, M.B. Dubl., D.C.H., D.P.H., D.P.M.: assistant psychiatrist (S.H.M.O.), Menston Hospital, near Ilkley.
DESSART, J. E., M.B. Lond., D.P.M.: assistant psychiatrist (S.H.M.O.), Storthes Hall Hospital, Kirkburton.
DUKE, P. A., M.D. Glasg., M.R.C.P., D.P.H.: assistant geriatrician (S.H.M.O.), Bradford A and B hospital groups.
EDWARDS, A. T., M.B. Aberd.: S.H.M.O. in pathology, Halifax hospital group.
IRONSIDE, W. McI. S., M.B. Aberd., F.R.C.S.E.: part-time consultant in otolaryngology, Huddersfield and Halifax area hospitals.
STAMP, R. A., M.B. Leeds, D.P.M.: assistant psychiatrist (S.H.M.O.), Menston Hospital, near Ilkley.
WHITE, D. C., M.B. Lond., F.F.A. R.C.S., D.A.: part-time consultant in anæsthetics, Hull A and B Hospital groups.

Manchester Regional Hospital Board:

MCLAREN, L. R., M.B. Cantab., F.R.C.S.: part-time consultant plastic surgeon, South Manchester group of hospitals.
SNOW, P. J. D., M.D. Manc., M.R.C.P.: consultant physician, Bolton and district group of hospitals.
WADDINGTON, G. H., M.R.C.S., D.M.R.D.: consultant radiologist, Lancaster and Kendal and Lancaster Moor groups of hospitals.
WILLIAMS, B. L., M.B. Manc., D.PATH.: consultant pathologist, West Manchester group of hospitals.

Births, Marriages, Deaths

BIRTHS

MORRIS.—On Oct. 3, at Queen Charlotte's Hospital, to Lucy (née Rivlin) and Norman Morris, M.D., F.R.C.O.G.—a son, Nicholas Humphrey, a brother for David and Jacqueline.